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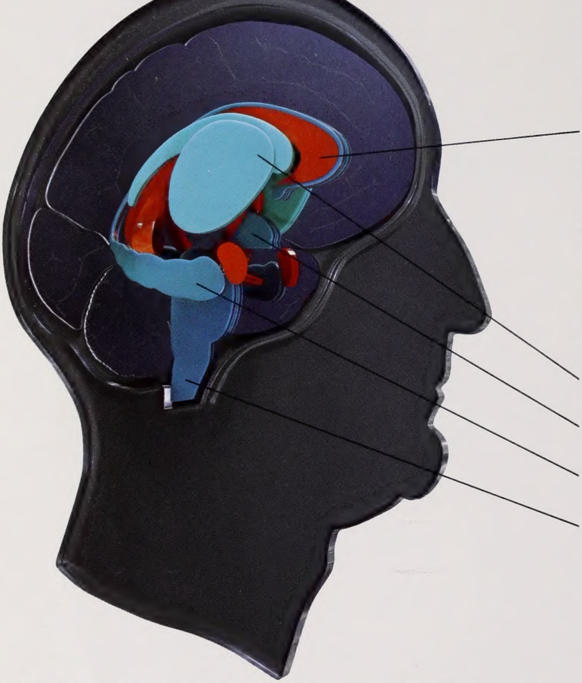

Active in the limbic system[1,2] where behavioral symptoms arise[1]... less active where neurotoxic effects occur[1-3]

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1. Borison R: Scientific Exhibit, 32nd Institute on Hospital and Community Psychiatry, Boston, MA, September 15-18, 1980. 2. Borison R: Lecture, Duke University Department of Psychiatry, Durham, NC, September 18, 1980. 3. Baldessarini RJ: Drugs and the treatment of psychiatric disorders in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, ed 6. New York, Macmillan Publishing Co Inc, 1980, pp 391,402,407.

Before prescribing or administering, see Sandoz literature for full product information. The following is a brief summary.

Contraindications: Severe central nervous system depression, comatose states from any cause, hypertensive or hypotensive heart disease of extreme degree.

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Precautions: There have been infrequent reports of leukopenia and/or agranulocytosis and convulsive seizures. In epileptic patients, anticonvulsant medication should also be maintained. Pigmentary retinopathy, observed primarily in patients receiving larger than recommended doses, is characterized by diminution of visual acuity, brownish coloring of vision, and impairment of night vision; the possibility of its occurrence may be reduced by remaining within recommended dosage limits. Administer cautiously to patients participating in activities requiring complete mental alertness (e.g., driving), and increase dosage gradually. Orthostatic hypotension is more common in females than in males. Do not use epinephrine in treating drug-induced hypotension since phenothiazines may induce a reversed epinephrine effect on occasion.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. Daily doses in excess of 300 mg should be used only in severe neuropsychiatric conditions.

Adverse Reactions: *Central Nervous System*– Drowsiness, especially with large doses, early in treatment; infrequently, pseudoparkinsonism and other extrapyramidal symptoms; rarely, nocturnal confusion, hyperactivity, lethargy, psychotic reactions, restlessness, and headache. *Autonomic Nervous System*– Dryness of mouth, blurred vision, constipation, nausea, vomiting, diarrhea, nasal stuffiness, and pallor. *Endocrine System*– Galactorrhea, breast engorgement, amenorrhea, inhibition of ejaculation, and peripheral edema. *Skin*– Dermatitis and skin eruptions of the urticarial type, photosensitivity. *Cardiovascular System*– ECG changes (see *Cardiovascular Effects* below). *Other*– Rare cases described as parotid swelling.

It should be noted that efficacy, indications and untoward effects have varied with the different phenothiazines. It has been reported that old age lowers the tolerance for phenothiazines; the most common neurologic side effects are parkinsonism and akathisia, and the risk of agranulocytosis and leukopenia increases. The following reactions have occurred with phenothiazines and should be considered whenever one of these drugs is used. *Autonomic Reactions*– Miosis, obstipation, anorexia, paralytic ileus. *Cutaneous Reactions*– Erythema, exfoliative dermatitis, contact dermatitis. *Blood Dyscrasias*– Agranulocytosis, leukopenia, eosinophilia, thrombocytopenia, anemia, aplastic anemia, pancytopenia. *Allergic Reactions*– Fever, laryngeal edema, angioneurotic edema, asthma. *Hepatotoxicity*– Jaundice, biliary stasis. *Cardiovascular Effects*– Changes in terminal portion of electrocardiogram, including prolongation of Q-T interval, lowering and inversion of T-wave, and appearance of a wave tentatively identified as a bifid T or a U wave have been observed with phenothiazines, including Mellaril (thioridazine); these appear to be reversible and due to altered repolarization, not myocardial damage. While there is no evidence of a causal relationship between these changes and significant disturbance of cardiac rhythm, several sudden and unexpected deaths apparently due to cardiac arrest have occurred in patients showing characteristic electrocardiographic changes while taking the drug. While proposed, periodic electrocardiograms are not regarded as predictive. Hypotension, rarely resulting in cardiac arrest. *Extrapyramidal Symptoms*– Akathisia, agitation, motor restlessness, dystonic reactions, trismus, torticollis, opisthotonus, oculogyric crises, tremor, muscular rigidity, and akinesia. *Persistent Tardive Dyskinesia*– Persistent and sometimes irreversible tardive dyskinesia, characterized by rhythmical involuntary movements of the tongue, face, mouth, or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements) and sometimes of extremities may occur on long-term therapy or after discontinuation of therapy, the risk being greater in elderly patients on high-dose therapy, especially females; if symptoms appear, discontinue all antipsychotic agents. Syndrome may be masked if treatment is reinstituted, dosage is increased, or antipsychotic agent is switched. Fine vermicular movements of tongue may be an early sign, and syndrome may not develop if medication is stopped at that time. *Endocrine Disturbances*– Menstrual irregularities, altered libido, gynecomastia, lactation, weight gain, edema, false positive pregnancy tests. *Urinary Disturbances*– Retention, incontinence. *Others*– Hyperpyrexia; behavioral effects suggestive of a paradoxical reaction, including excitement, bizarre dreams, aggravation of psychoses, and toxic confusional states; following long-term treatment, a peculiar skin-eye syndrome marked by progressive pigmentation of skin or conjunctiva and/or accompanied by discoloration of exposed sclera and cornea; stellate or irregular opacities of anterior lens and cornea; systemic lupus erythematosus-like syndrome.

Dosage: Dosage must be individualized according to the degree of mental and emotional disturbance, and the smallest effective dosage should be determined for each patient. *In geriatric patients with multiple symptoms such as agitation, anxiety, depressed mood, tension, sleep disturbances, and fears* the usual starting dosage is 25 mg t.i.d. and the dosage ranges from 10 mg b.i.d. to q.i.d. in milder cases to 50 mg t.i.d. or q.i.d. for more severely disturbed patients; the total daily dose ranges from 20 mg to a maximum of 200 mg.

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Gastric Fundopyloric Relationships: A Discussion prompted by "Vagal Stimulation and Inhibition of Acid Secretion and Gastrin-Release—Which Aspects are Cholinergic"[24]

DONAL F. MAGEE, M.D., PH.D.

Abstract

When it is realized that neither the Heidenhain pouch nor the vagally denervated antral pouch is totally denervated, it becomes unnecessary to invoke inhibitory vagal fibers or hormones to explain the elevations in serum gastrin seen after atropine or truncal vagotomy. This discussion is an examination of the above contention and of the evidence for a neuronal connection between fundus and pylorus.

Discussion

For several years, many workers have been concerned that, after atropine and after vagotomy, blood gastrin levels are increased (17, 28, 34, 58) above control in man and dogs. This has been seen during feeding and after insulin hypoglycemia (16). Several early workers had noted an increase in daily Heidenhain pouch secretion (15, 51) and others have noted an increase in gastrin stimulated Heidenhain pouch secretion following bilateral truncal vagotomy (14, 56).

The above, needless to say, have not been the findings of all, for example, Walsh, Csendes and Grossman (56) found no increase in basal serum gastrin and a reduced increase, together with an augmented Heidenhain pouch acid secretion following vagotomy in fed dogs. They have concluded that a hormone other than gastrin was responsible for this. Nilsson et al (42) found that atropine abolished Pavlov pouch secretion and reduced gastrin levels in sham fed dogs, that is, it depressed the vagal release of gastrin.

Despite some contrary evidence, there now seems to be no doubt that, in both man and dog, atropine and vagotomy do raise circulating levels of gastrin following feeding, and vagotomy probably does raise acid output from Heidenhain pouches in animals given pentagastrin. This is paradoxical because there is abundant evidence that vagal stimulation causes gastrin secretion (Uvnäs) (55). The contrary findings may be explained for the most part by: large doses of atropine (10), which are known to depress gastrin production, by acidification of antral mucosa in continuity with the main stomach or by inaccurate plasma gastrin determinations.

The explanations advanced for this apparent paradox have been:

(a) Since all of these drugs and procedures not only elevate gastrin, but also depress acid secretion, the absence of antral acid inhibition explains this phenomenon.
(b) Atropine blocks vagal fibers which inhibit gastrin production. This hypothesis implies the existence of noncholinergic vagal fibers which stimulate gastrin secretion because the evidence is very good indeed that vagal stimulation does release gastrin in most experimental animals.
(c) Atropine blocks vagal fibers which cause release of a hormone which depresses the action

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of gastrin on the parietal cell (the vagogastrone of Grossman et al) (23).

(a) can be dismissed quickly, since the effects of atropine on plasma gastrin are seen in animals with separated innervated antral pouches (7). Several workers (Feldman et al) (17) have kept the intragastric pH constant and have reproduced the phenomenon. Alkalinization of the antrum does not cause gastrin release measured either directly by immunoassay or indirectly by secretion from a Heidenhain pouch (26). Furthermore, the idea defies logic, an increase in fasting gastrin, such as occurs after vagotomy, achlorhydria (20) and other conditions of reduced acid secretion, can only be explained by some stimulus and not by absence of the brake, because fasting gastrins are not high in normal people or animals when acid secretion is frequently very low and antral pH therefore high.

The other two theories are based on a common oversight which has set back gastrointestinal physiology for years, which is that the Heidenhain pouch is a denervated pouch. It is not. It has full sympathetic and perhaps other innervation. This means that a response in a Heidenhain pouch seen after some manipulation to the antrum, even following vagotomy, is not proof of a hormonal mechanism. Several years ago the term "separated fundic pouch" was introduced to avoid the assumption of complete denervation. This seems to be forgotten now.

The question of cholinergic inhibitory fibers, to gastrin secretion, that is, the rise in serum gastrin after atropine, implies noncholinergic vagal fibers which stimulate gastrin production. There is ample evidence both direct (immunoassay) and indirect (H^+ secretion from Heidenhain pouches) in man and dogs that vagal stimulation, [electrical (10, 19, 48), sham feeding (37, 42, 46), and hypoglycemia (50)] do increase gastric secretion both directly as well as indirectly through the gastrin mechanism. But the question remains is this cholinergic? Langlois and Grossman (37) found that pylorectomy greatly reduced the stimulatory effect of bethanecol on Heidenhain pouches in dogs. Robertson et al (46) established that intrapyloric acetylcholine would stimulate vagotomized pouch acid secretion, but neither application to the mucosa of the fundic pouch nor intravenous acetylcholine could reproduce this effect. Kim (32) showed that the effect of acetylcholine in the antrum and also of intravenous methacholine on Heidenhain pouch secretion was significantly diminished by acidification of the antral pouch. Antinone et al (2) also have reported that antral acidification depresses the effect of intravenous methacholine. Tepperman et al (53) and Jackson et al (29) have shown that bathing the antral mucosa with ACh raises blood gastrin. Both Booth et al (4) and Hirschowitz and Gibson (27) have shown increased serum gastrin after intravenous acetylcholine and urecholine respectively. It seems clear, therefore, that the vagi do release antral gastrin and so do cholinomimetics whether administered intravenously or applied topically. Perhaps, however, this action of cholinomimetics is nonspecific. Davenport et al (8) have shown that the strong solutions of acetylcholine needed to stimulate antral gastrin release, result in the entry of plasma into the gastric lumen, but even this seems to be specific since it is blocked by atropine and accentuated by physostigmine. Succinylcholine chloride failed to produce the effect. Kim (32) found that neither choline nor nicotine applied to the antral mucosa would cause Heidenhain pouch acid secretion. It has been claimed that bile salts (Bedi et al) (3) stimulate antral gastrin release, but it is argued that this cannot be a nonspecific surface active phenomenon since sodium lauryl sulfate was without effect. In this paper, even the claimed increase in acid secretion from the Heidenhain pouch was of very dubious significance. It seems to me, therefore, that the existing evidence is heavily in favor of a direct specific cholinergic action of the vagi on the "G" cells in the antral mucosa. There is good evidence that atropine and ganglionic blocking agents can block the vagal release of gastrin (38, 42, 56). There is also ample evidence that the action of gastrin on the parietal cell is highly sensitive to atropine but not to ganglionic blocking agents (13, 22, 39, 43). Herein lies, in my view, the explanation for the finding that small doses and large doses of atropine have different effects.

The vagal release of gastrin is the ordinary muscarinic action of acetylcholine released from postganglionic parasympathetic nerves. The action of gastrin on the parietal cell is different and in part, because of its remarkable sensitivity to atropine (in dogs at least) and its resistance to ganglionic blocking agents, has characteristics similar to those of muscarinic ganglionic stimulants. In other words, small doses of atropine block the peripheral muscarinic ganglionic-like action of gastrin and large doses the ordinary muscarinic action of acetylcholine on the "G" cell. This explains why after large doses of atropine gastrin levels following sham feeding fall (17, 42, 55), but it does not explain why gastrin levels rise after small doses of atropine (28), or why there seems to be no positive relationship between plasma gastrin levels and acid secretion (33). I believe there is a relationship but it is a negative one, that is, in steady state experiments if an agent is given which depresses the parietal cell sensitivity to gastrin and perhaps cholinomimetics, plasma gastrin will rise. This is the case with atropine, catecholamines (49), cimetidine, etc (18, 45). The rise, according to Trudeau and McGuigan (54), seems to be roughly proportional to the extent of the depression in the maximal stimulated acid secretion (for example, in achlorhydria in man and in rats after fundic resection (1) basal gastrin levels are very high). This must mean that the sensitivity of the parietal cell to gastrin is in some way signalled to the "G" cell. Kondo and Magee (35) in recent studies have shown that reduction of the sensitivity of the Heidenhain pouch mucosa by cooling increased the secretion from the main stomach. This same phenomenon is the likely explanation for the recent claim that hypoglycemia can liberate gastrin in the absence of the vagi (50). In these experiments only plasma gastrin levels were measured, but had gastric secretion been determined a decrease would almost certainly have been found. Acid secretion from Heidenhain pouches has been shown to be depressed by insulin or hypoglycemia during: histamine stimulation (Karvinen and Karvonen) (31) meals (Necheles et al) (41) and methacholine (Burstall and Schofield) (6) and during basal secretion (Jemerin et al) (30). Taylor et al (52) have evidence for the corollary. They have found that bethanecol reduces the ability of bombesin to raise serum gastrin, that is, a bethanecol induced increase in parietal cell sensitivity has reduced the sensitivity of the "G" cells to a stimulant. The work of Hirschowitz and Gibson (27) corroborates this contention even more strongly. They have used doses of bethanecol which of themselves do not stimulate the parietal cell but are well known to augment the action of gastrin on the cell. These reduce the gastrin response to both 2DG and bombesin.

Atropine itself cannot be a direct gastrin stimulant or releaser since it does not raise basal blood gastrin in either dog or man nor does it raise blood gastrin in achlorhydrics whose secreting mucosa is already maximally depressed (42, 58) and blood gastrin already high.

The above does not explain how vagotomy can raise gastrin stimulated Heidenhain pouch secretion (14) and plasma gastrin. There are two possible explanations for this phenomenon; the first, vagotomy, by depressing the parietal cells in the main stomach reflexly raises plasma gastrin, as discussed above for other parietal cell depressants, which in turn increases Heidenhain pouch secretion. The fact that lack of stimulus to the acid secreting mucosa is important and not removal of some vagal inhibitory mechanism is borne out by the elevation in plasma gastrin seen after highly selective vagotomy which spares the vagal supply to the antrum (50). With this preparation, Hirschowitz et al (27) have found much greater increases in serum gastrin after 2-deoxy-d-glucose (2DG) than in animals with normal fundic innervation. The curve relating gastrin to acid was much less steep in the vagotomized animal, that is, the sensitivity of the parietal cell to gastrin was reduced. The second possible explanation is that vagotomy may interrupt part or all of an inhibitory pathway between parietal cell (42) and "G" cell. We think partial interruption more likely, since cooling Heidenhain pouch mucosa will raise fistula gastric secretion and cooling the main stomach mucosa (fistula) will raise pouch secretion. The latter is depressed by bilateral cervical vagal block (35).

There is good evidence not only that a depressed ability to secrete acid raises gastrin levels, but also that a depressed pyloric antrum increases the sensitivity of the parietal cell. Ragins et al (44) claim that antrectomy increased the secretory effect of histamine on Heidenhain pouches. Debas et al (9) found a steeper plasma gastrin concentration-acid secretion curve after denervation of the antrum than before. They ascribed this to vagal denervation, but actually their procedure was much more extensive. This is so also of the experiments of Tepperman (53), who found that denervation of the antrum depressed sham fed secretion from the main (innervated stomach) and blood gastrin levels but not Heidenhain pouch acid. Pepsin, in fact, was raised. In a paper, so far largely overlooked (34), we have found that antral depression by cooling or local anesthetics raises the fundic mucosal sensitivity to pentagastrin, but not to histamine. This effect was unaffected by vagal block or by acidification of the antrum but reproduced by β-adrenergic blockers and, therefore is, based on our experiments and in part those of Ragins et al (44), Debas et al (9) and Tepperman et al (53), a demonstration of sympathetically mediated tonic depression of parietal and chief cell responsiveness. Sjödin (47) has evidence for the corollary, namely that an increase in the sensitivity of the antral gastrin mechanism causes a decrease in

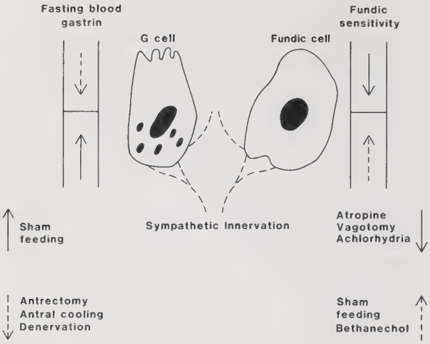

FIG. 1. The hypothetical reciprocal relationship between "G" cell secretion and parietal cell sensitivity. Levels of blood gastrin and fundic sensitivity are shown on the left and right respectively—factors which push these up or down are shown by the arrows. The arrows indicate that factors which raise the right (⇡), lower the left (⇣) and vice versa (↓,↑).

sensitivity of the fundus in that he has found that sham feeding depresses the Heidenhain pouch's gastrin stimulated acid secretion. This effect as might be expected was abolished by truncal vagotomy. The existence of such a mechanism was suggested by Gregory (21) who credits the inconclusive nature of efforts to decide for or against an antral inhibitory hormone to lack of attention to the state of the antral innervation.

In the course of the conflicting claims that made up that controversy, this is rarely made clear and therefore it is impossible to evaluate the conclusions. In most, only vagal denervation is attempted or mentioned, DuVal et al for example (12). Possible exceptions are the studies of Harrison et al (24) and Woodward et al (57). Harrison et al transplanted the distal half of the antrum into the colon leaving the proximal part in continuity. Subsequent removal of the proximal part increased the daily secretion from a Heidenhain pouch. Woodward et al translocated the proximal part to the colon and subsequently removed the distal half getting no increase in secretion probably because in translocating the proximal portion the distal was effectively denervated, while the Harrison et al pouch was not. Harrison et al argued that an inhibitory hormone had been removed with the antrum and Woodward et al that such a hormone did not exist. Dragstedt et al (11) later repeated the experiment of Harrison et al exactly and now did get an increase in pouch acid secretion. Animals with excluded antra have been shown to be much more susceptible to experimental peptic ulceration. Broome and Olbe (5) have shown a decrease in the maximal histamine response after antrectomy. This may not be the contradiction to the above that it seems since all their subjects were duodenal ulcer patients in whom basal blood gastrin levels and acid secretory capacity are abnormal to start with. Our data (34) and our interpretation of other's (9) support Gregory's view given above.

In light of our findings (34) and those of Debas (9), acidification of the antrum in consequence of the depression of gastrin release might also increase the sensitivity of the parietal and chief cells to circulating gastrin provided the sympathetic innervation to both antral and Heidenhain pouches is intact. We have found an increase, at the time inexplicable, in Heidenhain pouch pepsin secretion on antral acidification in pentagastrin stimulated dogs (40). This is seen also in Tepperman et al (53) and in our antral cooling experiments (34). In the latter, propranolol significantly raised pentagastrin stimulated pouch pepsin which suggests that the usual failure of pentagastrin to stimulate Heidenhain pouch pepsin could be due to tonic unopposed β-adrenergic inhibition.

Conclusion

There is good but scattered evidence for the idea that the sensitivity of the secreting fundic mucosa induces compensatory changes in the secretory activity of the "G" cells. Thus the activity of secretory suppressants like atropine, glucagon, catecholamines, etc. in raising blood gastrin levels can be explained as consequential to depressed fundic secretion rather than as evidence for inhibitory vagal fibres or hormones. There is further good evidence that diminution of the sensitivity of the antral "G" cells is accompanied by an increase in the sensitivity of the parietal cells. Antral innervation other than vagal seems to be responsible for this. This mechanism summarized in Figure 1 explains the increase in Heidenhain pouch secretion following vagotomy and it also explains why in past experiments, purporting to show the existence of an antral inhibitory hormone, removal of the half antrum in continuity, increased pouch secretion. The tacit but still prevalent assumption that the vagi are the only nerves to the stomach has greatly retarded gastric physiology and is responsible for the unresolved confusion which still surrounds the attempts in the recent past to explain antral inhibition of acid secretion.

That hormone production and the secreting cell population increase when the target organ is depressed is a general principle in endocrinology. There is, in my view, no evidence that the stomach is an exception and a lot, if looked for, that it is in conformity with this principle.

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Behavior of Internal Tibial Torsion in Infancy

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Abstract

Lower limb torsional deviations may begin as a result of local pressures during fetal intrauterine modelling. Others may follow or be enhanced by prone position lying in early infancy before development of the ability to change positions spontaneously. Internal tibial torsion and metatarsus adductus represent a common combination with others occurring less frequently. The early natural history of these developmental deformities leaves questions about spontaneous correctability and whether or when treatment should be considered.

This paper reports a limited study of 99 infants with internal tibial torsion who were observed in an orthopaedic consultation clinic during their first year of life. At about one year of age, half of them underwent sufficient spontaneous improvement not to require treatment. The other half were referred for Denis-Browne splint therapy. In the group in which deformity persisted, a significantly greater number had bilateral internal tibial torsion and also a greater number were associated with metatarsus adductus.

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The infant at birth exhibits variable evidences of developmental intrauterine modelling of the skull, face, trunk, and often the lower limbs. Since these changes are presumed to have occurred after normal genesis, their severity may be related to factors in the intrauterine environment such as oligohydramnios, uterine muscle tone, and maternal body habitus (1).

Infants examined in the newborn nursery often show mild inward or outward orientations of the lower limbs (Figs. 1, 2). These children have not yet assumed the prone sleeping position which later exerts a complementary role. In the photograph showing the newborn placed into the prone position, there is obvious lack of adaptation of the lower limbs to this attitude (Fig. 3). This is in significant contrast to the older infant shown in Figures 4, 5 where the infant's preference in limb placement has better adaptation to the prone situation. An infant shown in Figure 6a, b exhibits striking head change following the unusual circumstance of always lying in the supine position (2). The response of growing parts of the skeleton to continuous pressure is a normal characteristic. The infant is at particular risk for such adaptive change during the final stages of intrauterine development as well as in the early infantile period before attaining ability to change positions. Spontaneous improvement cannot be expected until there is escape from entrapment, either from a confining intrauterine environment or equally restraining prone sleeping placement. As the opportunity for spontaneous turning arises and is explored, the prior adaptive limb alterations diminish and disappear proportionately.

The questions for which there have been uncertain answers, are "what is the natural history of these modelling deformities?" (3) "Will they disappear with growth?" "Do they require treatment?"

This presentation deals with some of the experiences in an orthopaedic consultation clinic to which young patients are referred mainly from well baby centers and public school health services. Review of a three-month census showed that internal tibial torsion represented the largest single category (27%), intoeing associated with increased femoral anteversion (14%) the sec-

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Presented at the Orthopaedic Section of the American Academy of Pediatrics Annual Meeting, October 25, 1980, Detroit, Michigan.

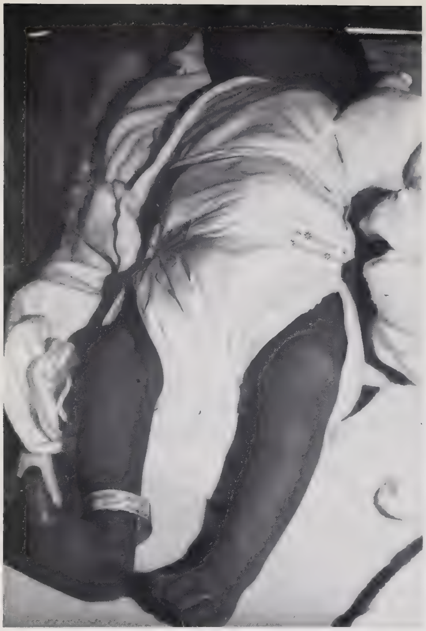


FIG. 1. Photograph of an infant in the newborn nursery lying in supine position demonstrating foot and leg rotational attitudes. The right has an external orientation while the left points inwardly.

ond largest, and external rotation limb attitude and external tibial torsion (5%) the third. There was a wide range of other assorted orthopaedic problems in diminished numbers. The infant age group was predominant and undoubtedly represented a bias in the large numbers of torsional problems.

The policy of the clinic in the management of internal tibial torsion is observational during the first year of life. It changes to referral to the regular children's orthopaedic clinic for more definitive handling (usually with a Denis-Browne bar and attached shoes) when the tibial torsion persists beyond this period.

This study does not include observation without "treatment" beyond this point, so that the natural history of tibial torsion relative to further spontaneous correction is not available.

The method of measurement employed for the determination of tibial torsion was a clinical one. With the proximal tibia aligned in the frontal plane (using the patella, plane of motion of the knee joint, as well as the tibial tubercle for this orientation) the position of the foot indicated the direction and magnitude of the tibial torsion. Maximum dorsiflexion of the foot stabilized it in the ankle joint making it most reflective of the

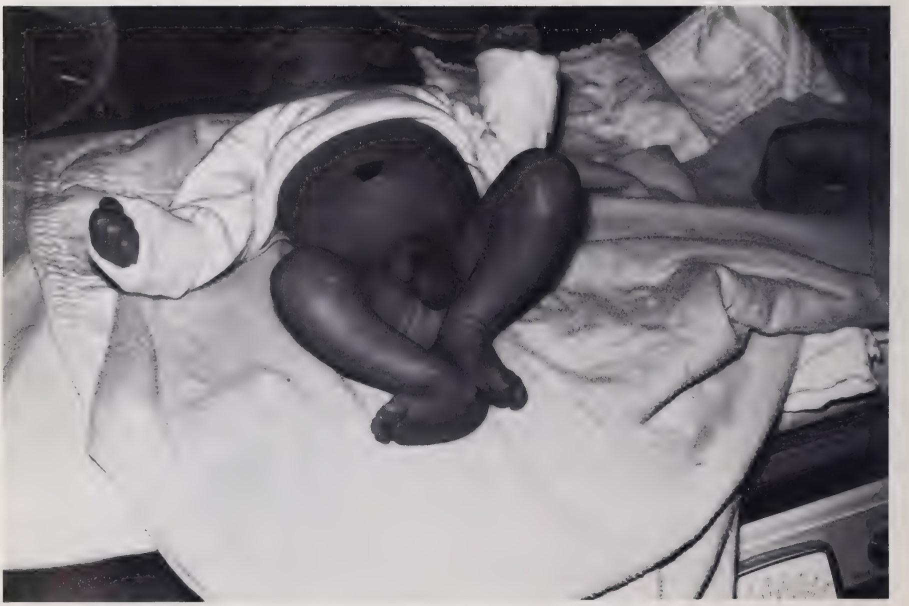


FIG. 2. This infant lies with both lower limbs externally oriented, the right somewhat more prominently. The right foot suggests the appearance of a calcaneovalgus attitude by its increased dorsiflexion.

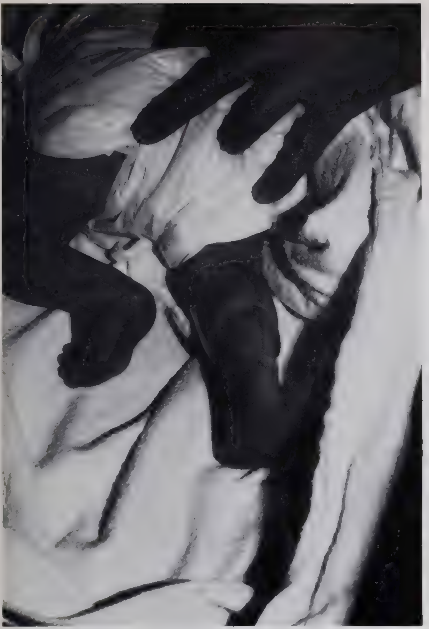


FIG. 3. This infant, previously shown in Fig. 1, has now been turned over. The outwardly rotated right leg is now lying neutrally and the left inwardly inclined limb is externally maintained suggesting absence of fixed skeletal deformity.

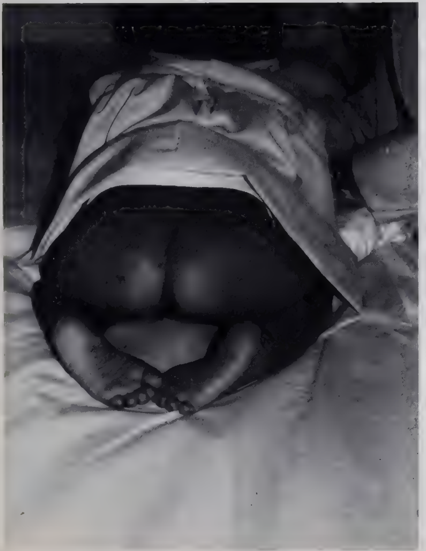


FIG. 4. This older infant shows the result of adaptation of inwardly rotated lower limbs to the prone lying position.

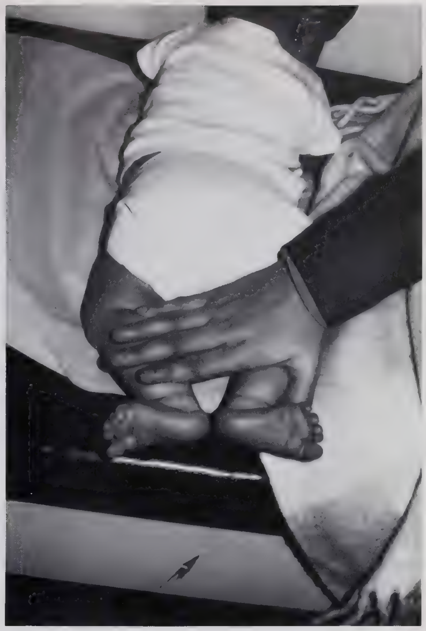


FIG. 5. This older infant shows the result of adaptation of outwardly rotated lower limbs to the prone lying position. (Placement of hand discouraged motion while the photograph was taken).

distal tibial torsional status. When the foot pointed straight forward, the torsion was 0°; when it pointed inward or outward the torsion was internal or external. With associated metatarsus adductus this method required using the hind foot for torsional orientation.

An alternate clinical method also positioned the proximal tibia as described above but instead of using the foot as a tibial torsional indicator took advantage of the frontal relationship of the ankle malleoli. In the neutral situation, the lateral malleolus is about 15° posterior to the medial malleolus; with internal tibial torsion the lateral malleolus comes forward; with external tibial torsion the lateral malleolus recedes further posteriorly. In the period 1976–1977, there were 99 children with ITT who returned for a second or, at times, third evaluational visit following prior observational management.

At initial visit, the average age of the patients was 6.1 months (range from 2 to 22 months) 56% of the group was under 6 months and 86% under 9 months of age (Table I).

At last followup examination, the average age of the children was 13.1 months (range from 6 to 37 months) 55% of the group was between 10 to 15 months (Table II).

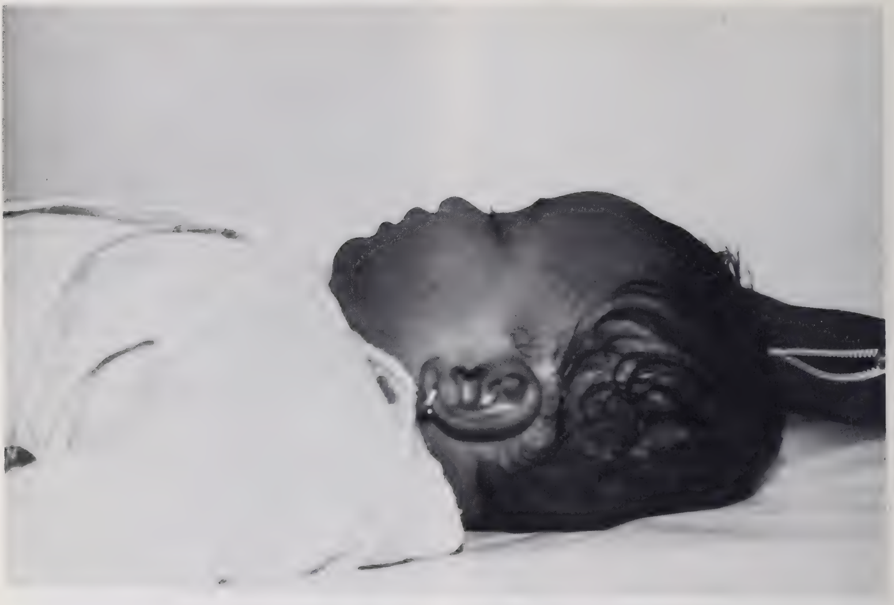


FIG. 6a This infant's supine sleeping attitude shows the area of contact between the back of the head and the bed.

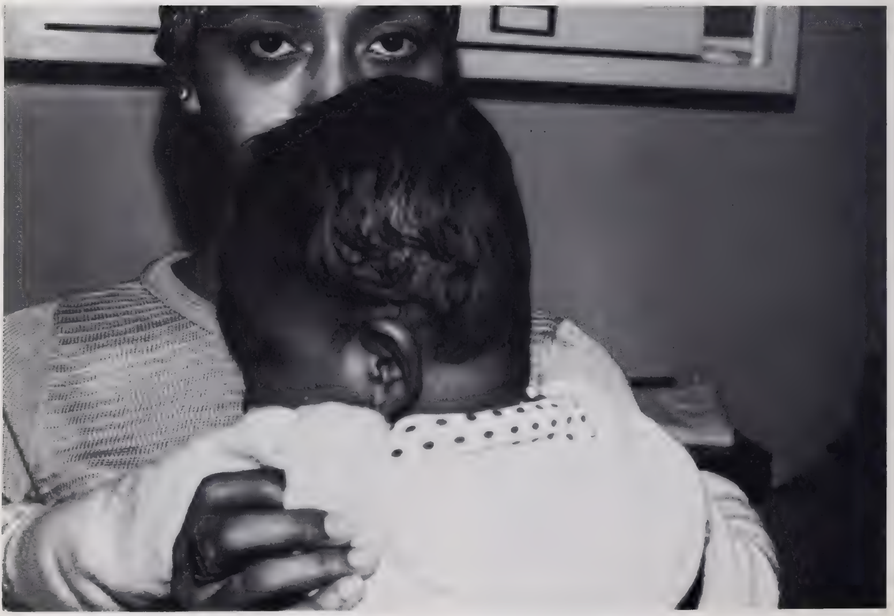


FIG. 6b The modelling influence of the persistent head attitude is demonstrated in the prominent flattening of the back of the head.

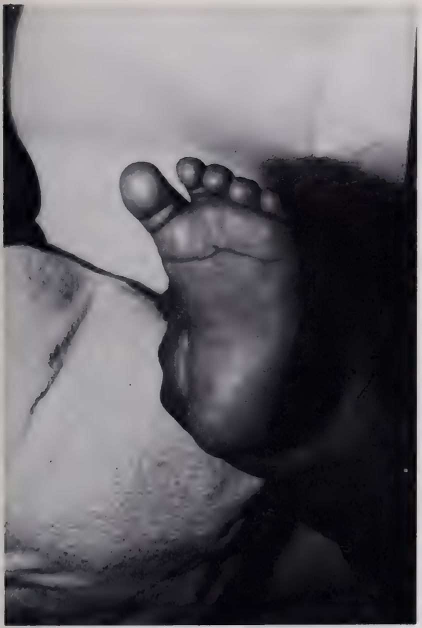


FIG. 7a This infant's foot shows the features of metatarsus adductus. Essentially it consists of a neutrally aligned heel with an inwardly deviated forefoot.

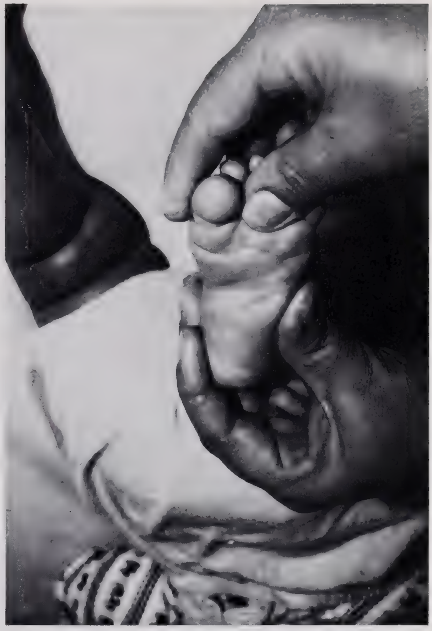


FIG. 7b This photograph shows the flexibility of this infant's metatarsus adductus to mild manipulation. The parent had been instructed to stabilize the heel with one hand and direct lateral pressure to the forefoot with the other.

The interval between the initial and final visits averaged seven months (range three to 25 months).

Ot the 99 children in the study, 54 were females and 45 males. 51.5% (51 children (29 females 22 males)) had bilateral involvement at the initial visit. 38% (38 children 19 females 19 males)) had left side and 10% (10 children (6 females 4 males)) right side involvement.

At the time of revisit, it was determined that 54 children still had their torsion and were referred to the Orthopaedic Clinic for Denis-Browne splint

TABLE I

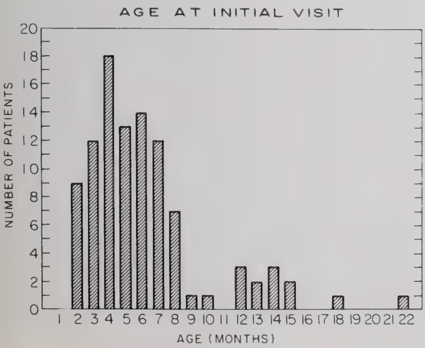
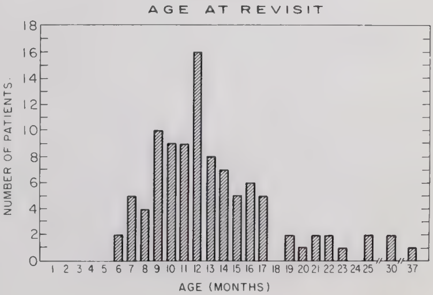


TABLE II



and that 45 children had undergone sufficient spontaneous improvement not to need treatment.

An effort was made to determine whether any special characteristics were present in either group that could be used as prognostic markers. Of the 54 children who were subsequently referred for treatment 61% (33) were bilateral on initial examination, 33% (18) had left sided, 6% (3) right sided involvement. Of the 45 children who improved spontaneously, 40% (18) were bilateral, 44.4% (20) left sided and 15.6% (7) right sided involvement.

A related observation concerned the association of (Fig. 7a, b) metatarsus adductus with internal tibial torsion. In this group of 99 children, it occurred 40 times (40%). On further subdivision, it was noted 26 times (65%) with bilateral torsion, five times (12.5%) with right side and nine times (22.5%) with left side involvement.

Examined separately, the group which failed to resolve spontaneously showed metatarsus adductus in association with bilateral internal tibial torsion 19 times (47.5%) with left side 6 times (15%) and right side 2 times (5%). The group which did improve spontaneously showed associated metatarsus adductus with bilateral tibial torsion 7 times (17.5%) left side 3 times (7.5%) and right side 3 times (7.5%).

Conclusions

In approximately one hundred infants, one half had bilateral involvement, about 40% had unilateral left side and 10% unilateral right side involvement.

This small experience in the management of internal tibial torsion suggests an almost 50% rate of spontaneous improvement in children between an average age of 6 months and an average age of 13 months.

In the group undergoing spontaneous improvement there was no difference between boys and girls. Although there were representations from the bilateral and unilateral varieties, the unilaterally affected children made up a larger segment (60%) suggesting a better prognosis than those with bilateral torsion (statistically significant).

In general there was a 40% (40 children) association of metatarsus adductus with internal tibial torsion. The group undergoing spontaneous improvement had half as much (13 children) associated metatarsus adductus than did the group requiring treatment (27 children). The association of metatarsus adductus with internal tibial torsion suggested a poorer prognosis for spontaneous improvement (statistically significant).

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Pleomorphic Atypical Thyroid Adenoma Arising in Struma Testis: Light Microscopic, Ultrastructural and Immunofluorescent Studies

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Abstract

We report a monophyletic mature teratoma of the testis (struma) associated with a thyroid adenoma. The tumor displayed light and electron microscopic similarities to the normal thyroid and to thyroid tumors. Presence of thyroglobulin in the tumor tissue was demonstrated by immunofluorescence. This case illustrates an exceedingly rare variant of testicular teratoma and demonstrates application of the immunofluorescence technique in diagnostic surgical pathology.

Thyroid tissue occurs exceedingly rarely in teratomas of the testis. Unlike the ovarian counterpart, struma testis is an entity practically unheard of, as also are the solid thyroid tumors, adenoma and carcinoma, arising therefrom. The authors had the opportunity of examining a testicular tumor which they believe qualifies for the designation given in the title of this report.

Case Report

A 68-year-old man was hospitalized because of prostatic obstruction and a dull aching pain in the scrotum of a two year duration. A 5 × 5 cm mass was palpated in the upper pole of the right testicle. It was of a hard consistency and slightly tender. The upper pole of the epididymis could not be felt separately. Lower parts of the testis and epididymis were felt normal. The left testis and epididymis and both spermatic cords were unremarkable. The prostate was diffusely enlarged. Otherwise, the general physical examination did not disclose significant abnormal findings. The thyroid gland was not enlarged and there was no hyperthyroidism. The clinical impression was that of chronic epididymitis and benign prostatic hyperplasia. The patient refused surgical intervention at that time. When seen eight months later, the size of the testicular mass remained unchanged, and he consented to surgery. Right orchiectomy, needle biopsy of the prostate, and left vasectomy were performed. The postoperative period was uneventful. Four years and three months later the patient had prostatectomy for the obstructive hyperplasia, and he had no evidence of a recurrent of metastatic tumor at that time.

Pathologic Findings

The prostatic biopsy and vasectomy specimens were unremarkable.

Testicular Tumor

Gross: The testis measured 6 × 4 × 4 cm. The tunica vaginalis was freely movable. The cut surface revealed virtual replacement of the testis by a microcystic tumor. The cystic spaces varied in size from less than 1 mm to 1 cm. They were filled with a light brown gelatinous material. At the periphery of this mass, at upper pole of the testis,

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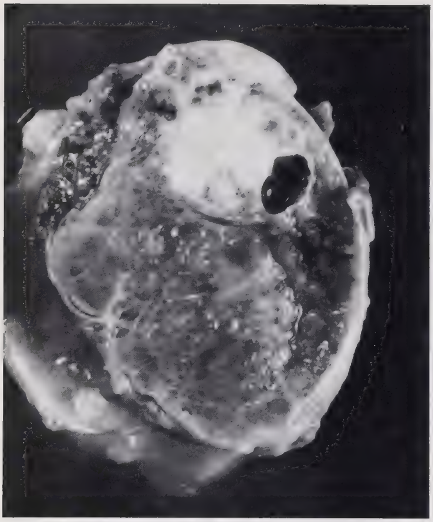

FIG. 1. Cut section of the struma showing innumerable follicles, many cystically dilated cystically dilated, virtually replacing the entire testis. The adenomatous area is seen in the upper pole. Separate normal epididymis.

there was a solid pale gray area measuring 2 × 2 cm (Fig. 1). It was hard in consistency and of an irregular outline, merging in places with the surrounding microcystic tissue. No erosion of the tunica or extracapsular extension of the tumor was noted. Remnants of the testicular tissue were seen at the periphery. The epididymis was normal in shape and consistency.

Material and Methods

The tissues were fixed in 10% formalin and processed routinely. For light microscopic examination the slides were stained with hematoxylin-eosin, periodic acid-Schniff without and with prior digestion with diastase, mucicarmine, trichrome, reticulin, and Fontana-Masson.

For electron microscopy, multiple 1 mm cubes of tissue were taken from various areas of the formalin-fixed tumor. They were postfixed in osmium tetroxide, dehydrated in graded alcohols and propylene oxide, and embedded in Epon. Thick sections were stained with toluidine blue. Thin sections were stained with uranyl acetate and lead citrate and examined with a Phillips 300 electron microscope.

Indirect immunofluorescent technique was used to detect the presence of thyroglobulin in the tumor tissue. Serum high in antithyroglobulin content (over 1:100) was obtained from three patients with Hashimoto's thyroiditis, pooled, and stored at −20 degrees C in aliquots of 0.1 ml. Tumor sections were cut from the paraffin blocks. The sections were deparaffinized and washed overnight in phosphate buffered saline (PBS), pH 7.15. Substrate controls consisted of similarly prepared sections of thyroid tissue and of testis and dilated rete testis from other surgical specimens. Serum controls consisted of human serum not containing thyroglobulin antibody and pooled antithyroglobulin serum absorbed with minced fresh thyroid. The sections were overlaid with 1:10 dilutions of antiserum for 30 minutes at room temperature in a humidifying chamber. After a 15 minute wash with PBS, the tissue was flooded with fluorescein conjugated goat antihuman IgG (Hyland Laboratories, Costa Mesa, California). This conjugate had a fluorescein to protein molar ratio of 3.5 and was diluted with PBS containing 4% bovine serum albumin (BSA) so that the working solution contained 50 micrograms of specific antibody per ml. PBS with 4% BSA was also used to dilute antiserum and control sera. A final 60 minute PBS wash was followed by mounting the sections in buffered glycerol. Processed slides were viewed by incident light microscopy employing an FITC interference-excitation filter and a K530 barrier filter. An Osram HBO-200 high pressure mercury vapor lamp served as the light source.

Results

Light microscopy: The cystic portion of the tumor was composed of spaces filled with amorphous colloid eosinophilic material. Delicate branching trabeculae, lined by a single layer of cuboid or flat cells, divided the tumor into smaller compartments. Some areas had the appearance of normal thyroid tissue (Fig. 2). Focally, there was a granulomatous inflammation, evidently a reaction to a spilled colloid. The solid part of the neoplasm merged with the follicles (Fig. 3). Solid, trabecular, follicular, and papillary areas were seen (Figs. 3–6). The cells were of medium size, showing scant cytoplasm and round, ovoid or spindle nuclei. Cellular pleomorphism and atypia were moderate. Mitotic figures were easily found, none of them abnormal. The colloid stained positively with periodic acid-Schiff, both without and with prior digestion with diastase. One small area of the tumor was mucicarmine

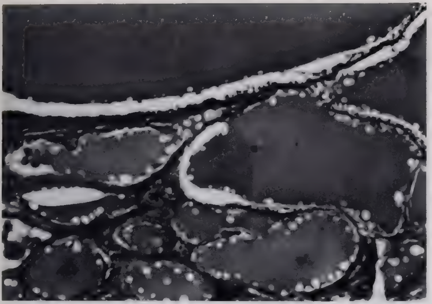

FIG. 2. Thyroid tissue with a cystically dilated follicle (top) (×100).

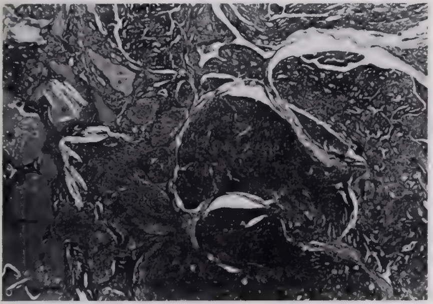

FIG. 3. The adenoma merging with thyroid follicles (left). Solid, follicular and papillary patterns are seen (×25).

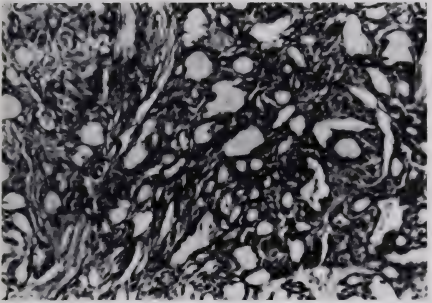

FIG. 4. An area of the adenoma which showed mucicarminophilia of the follicular contents (×100).

positive (Fig. 4). The Fontana-Masson stain was negative. No other teratomatous elements were identified. Remnants of the testicular parenchyma were seen focally at the periphery of the tumor. The seminiferous tubules were mostly atrophic and the Leydig cells were prominent.

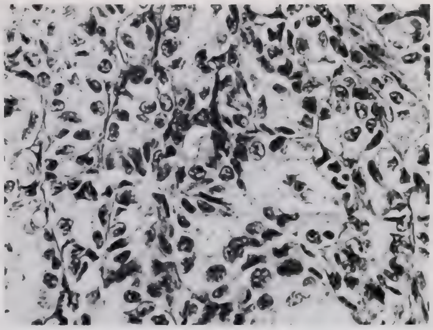

FIG. 5. Formation of small follicles with lumens. Moderate cellular atypism (×250).

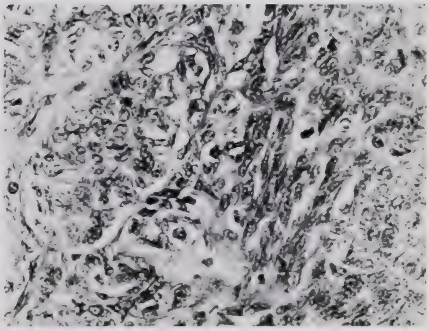

FIG. 6. Solid area of the tumor with poorly differentiated cells. A mitosis is seen (right upper) (×250).

Electron Microscopy

The predominantly follicular or cystic areas showed an epithelial lining composed generally of cuboid cells. (Fig. 7), abutting on a basal lamina and showing hemidesmosomal cytoplasmic densities at this abluminal surface. The intercellular (lateral) spaces showed sometimes "jigsaw" interlocking surfaces; they were occasionally distended, although more often narrow and bridged by desmosomal or intermediate intercellular junctions, or rarely, tight junctions. The luminal side of these cells showed frequent slender microvillous projections. No cilia were observed. The cytoplasm contained abundant free ribosomes, moderate amounts of rough endoplasmic reticulum, occasional mitochondria and smooth endo-

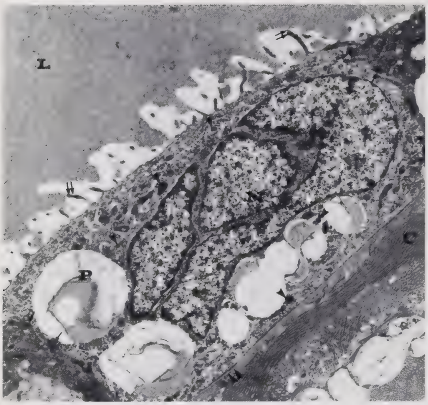

FIG. 7. Detail of the periphery of a follicle showing: convoluted nucleus (N) of the epithelial lining cell, intercellular junctions (arrows), secretory granules and lysosomes (arrowheads), phagolysosomes (P), microvilli (double arrows), follicular lumen with colloid (L), basal lamina (double arrowhead), and collagen (C) (×7320).

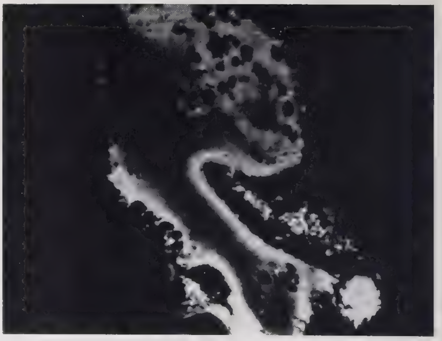

FIG. 8. Follicular area of the neoplasm showing immunofluorescent material after reacting with thyroglobulin antibody and labeled anti-human IgG (immunofluorescent microscopy) (orig. magnif. ×100).

plasmic reticulum, medium sized Golgi apparatus (usually supranuclear), and numerous electron-dense secretory granules and lysosomes. Some cells contained large phagolysosomes and lipid droplets. The nuclei were of variable size, round to oval, sometimes with deep cytoplasmic clefts, and usually contained a single nucleolus. The intraluminal secretory contents were homogeneous and finely granular. Solid areas of the tumor showed somewhat similar cellular characteristics; here, however, the secretory granules were not seen, the lysosomes were scant, the nuclei displayed greater irregularity in shape, and the intercellular spaces were narrow. Collagen was seen in the spaces between cell clusters. Amyloid was absent.

Immunofluorescence

Sections of control thyroid tissue demonstrated strong fluorescence of colloid material after reacting with thyroglobulin antibody, but not with the non-immune serum or absorbed serum. Areas showing similar fluorescence were clearly visible after the tumor sections had been processed with thyroglobulin antibody (Fig. 8), but not with the control sera. The testicular and rete testis tissues failed to show immunofluorescence with any serum.

Discussion

"Thyroid tissue is extremely rare in teratomas other than ovarian," wrote Willis in 1951 (1). Concerning different components of testicular teratoma, Ewing wrote in 1919: "Thyroid tissue is extremely rare, . . . but I have described four lobules of adult thyroid resembling the normal organ in the minutest details" (2). Accompanying microphotograph showed thyroid follicles surrounded by testicular tissue (2). In more recent publications based on large series of testicular teratomas, the thyroid component is not even mentioned (3–5).

In view of this rarity of testicular struma, the diagnosis of the tumor required adequate documentation. Light microscopic differential diagnosis includes a cystadenoma, known well as a tumor of the epididymis (6), but occurring occasionally also in the testis (7). The epididymal tumors occur most frequently in the area of head and present an intracystic papillary growth with a fibrous stroma. The epididymis in this case was normal and quite separate from the tumor. A single instance of intratesticular papillary cystadenoma has been reported (7), but did not resemble the present case. Rather, it was a single cyst with the intracystic papillations lined by cuboid and ciliated columnar cells. Papillary adenocarcinoma arising from mullerian epithelium of the appendix testis also shows a much different appearance from the tumor being studied (8). Rete testis origin of the tumor could also be discounted because of the presence of numerous cytoplasmic secretory granules and lysosomes (9). In addition to the light microscopic similarity of the tumor to the thyroid, the authors found ultrastructural features similar to those of normal thyroid (10–12), struma ovarii (13), and follicular carcinoma of the thyroid (14, 15). The secretory granules characteristic of the C cells of the thyroid (10), and carcinoids (13), were absent, and therefore an APUD-cell origin of the neoplasm could be ruled out. The production of immunofluorescence in the tumor after reacting with the thyroglobulin antiserum appears to be unequivocal evidence of the presence of thyroglobulin with the tumor and thus establishes the thyroid nature of the tumor cells. Thyroglobulin antibodies are usually species specific as well as organ specific (16). The authors' review of the literature failed to reveal any report of a similar case, with the possible exception of a tumor described by Pal and associates as a "calcifying malignant struma of the testis" (17). These authors reported an 8 cm cystic testicular mass in a 65-year-old man. The cyst contained a dirty viscous fluid and the wall was densely fibrous with calcification and ossification. Thyroid follicles and areas resembling follicular adenoma and papillary carcinoma of the thyroid were described and the interstitium was said to show clumps of tumor cells resembling the follicular lining cells. The appearance of epididymis was not mentioned. A dense opacity, about 6 cm in size, was visualized radiographically and interpreted as a calcified para-aortic lymph node metastasis. It was not biopsied, however, and thus there is no proof that indeed it was one. Regretfully, no follow-up of this patient could be obtained (18).

In this present case, the mucin production found in one area of the tumor is of interest. Mucicarmine positivity has been occasionally observed by the authors and by others in normal thyroid and in follicular adenomas of the thyroid; it also has been reported sometimes in thyroid carcinomas (19, 20).

The tumor lacked encapsulation. Its cells showed areas of at least moderate atypism, poor differentiation, and easily recognizable mitoses. Yet, despite these worrisome features, no vascular invasion was found, and there was no evidence of recurrent or metastatic tumor 4 years and 3 months postoperatively. Therefore, in view of the absence of absolute criteria of malignancy, the tumor is designated as an atypical adenoma and not carcinoma.

Only a minority of the so-called malignant ovarian strumas have been associated with metastasis, common sites of the spread being the bone and peritoneal surfaces (21). Many of the earlier cases reported as thyroid adenomas or carcinomas of the ovary were in reality carcinoids (21). The reasons for the rarity of thyroid tissue in the testicular teratomas are unknown.

This case illustrates the importance of the specific immunofluorescence technique as applied to the diagnostic surgical pathology. It is apparently the first reported case of a thyroid tumor the testis with the diagnosis supported by the finding of thyroglobulin in the tumor tissue.

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Evaluation of Pancreatic Exocrine Function with the Synthetic Peptide BT-PABA in Diabetes Mellitus

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It has been pointed out that pancreatic exocrine function is diminished in a high percentage of patients with diabetes mellitus (1), notably in patients with juvenile onset on insulin therapy (2). However, as pancreatic exocrine function is evaluated by the P.Z/C.C.K.-Secretin test (P-S test) in these patients, various problems arise; an insignificant number of cases, variations in results of evaluation, and different normal ranges arbitrarily set by individual investigators. Recently, a new test designated PFD (Pancreatic Function Diagnostant) which uses N-benzoyl-L-tyrosyl-p-aminobenzoic acid (BT-PABA) orally was developed and attention is focused on it (3). BT-PABA is a new synthetic peptide which is hydrolyzed specifically by chymotrypsin, one of the proteolytic enzymes secreted by the pancreas. The PFD is advantageous in several ways: it is easy to perform; it causes little discomfort to the patient; it is highly reproducible; and it shows a good correlation to the conventional P-S test (4, 5). For these reasons PFD has already been in widespread use.

The work presented here is an investigation which was undertaken in order to determine pancreatic exocrine function in patients with diabetes mellitus by the PFD test and to study how it is related to the residual pancreatic B cell function, the progress of diabetic microangiopathy, and the severity of diabetic autonomic neuropathy.

Subjects

The population of this study consisted of 63 diabetics and 11 healthy persons. The diabetics consisted of 16 patients with insulin-dependent diabetes mellitus (IDDM), 37 patients with non-insulin-dependent diabetes mellitus (NIDDM) and ten patients with diabetes mellitus with pancreatolithiasis (PaDM). As shown in Table I, the diabetics were further according to the staging of diabetic retinopathy; group of patients with mild microangiopathy (MA(−)) (presenting in Stage I or Stage II according to Scott) and group of advanced microangiopathy (MA (+)) (presenting in IIIb or higher Stage). It should be noted that the IDDM patients were limited to those who had onset under the age of 30 years, had no history of obesity, and were insulin-dependent from the onset. The diagnosis of NIDDM was made when the patient had primary diabetes mellitus other than IDDM. PaDM was defined as secondary diabetes mellitus with pancreatic calculus demonstrated by plane x-ray examination. Patients with 40 ml/min or lower creatinine clearance, those with remarkably impaired liver function and the aged over 70 years were excluded from the study.

Materials and Methods

Pancreatic exocrine function was evaluated after an oral PT-PABA load (PFD test). The solution of PFD (product of Eisai Co.) containing 0.5 g of BT-PABA (169.5 mg of PABA) was given with 250 ml of water after urination early in the morning and given another 250 ml of water after two hours. Urine samples were collected at one-hour intervals for two hours after administration and at two-hour intervals from the second till the sixth hour. Following the measurement of the urine volumes, part of the specimen was preserved in a refrigerator for later use in the determination of PABA. The patients fasted during the PFD test as a rule, but those on insulin therapy were allowed to take a light meal after injection of

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TABLE I

Primary Diabetes Mellitus	number of cases
Insulin-dependent (IDDM)	16
without advanced microangiopathy (MA(−))	11
with advanced microangiopathy (MA(+))	5
Non insulin-dependent (NIDDM)	37
without advanced microangiopathy (MA(−))	25
with advanced microangiopathy (MA(+))	12
Secondary Diabetes Mellitus	
Diabetes Mellitus with pancreatolithiasis (PaDM)	10

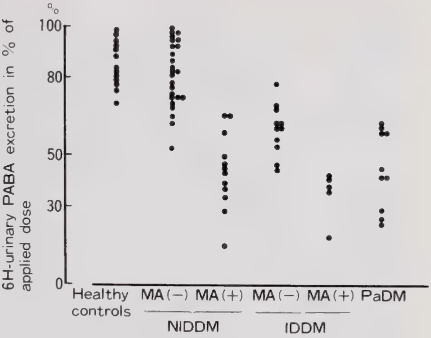

FIG. 1. Urinary PABA excretion (six hours collection) in healthy controls and various types of diabetes mellitus.

ordinal insulin dose following urination at the fourth hour and the PFD test was performed till the sixth hour. All drugs were withdrawn for at least 24 hours before onset of the PFD test.

The urine levels of PABA were determined according to the modification of Smith et al on the method of Brattom, Marshall et al. Pancreatic exocrine function was determined, using the cumulative urinary excretion of PABA as a parameter.

To exclude factors other than pancreatic exocrine function, the PABA absorption test was also performed in some patients by administering orally 169.5 mg of PABA similarly to the PFD test. The test results were evaluated exactly in the same way as in the PFD test.

Pancreatic B cell function was evaluated, referring to the total response area of C-peptide for 120 minutes (ΣCPR) after a 50-Gm oral glucose load as a parameter. The level of serum C-peptide was determined by radioimmunoassay, based on the double antibody method. The mean ΣCPR in healthy persons was 17.8 ± 2.0 (Mean ± SD).

The severity of autonomic neuropathy was expressed by the coefficient of variation (CV) of the R-R intervals of the resting ECG. The mean CV in healthy persons was 5.8 ± 2.1. The lower the CV is, the more marked the autonomic neuropathy is (6).

Results

Figure 1 summarizes the PFD test results obtained in IDDM, NIDDM and PaDM patients and healthy persons. In the PFD test the cumulative recovery of PABA in the six-hour urine was determined. All the diabetics included in the present study were receiving treatment and no untreated patients are included. The mean six-hour recovery of PABA was 85.8 ± 8.6% in the group of healthy persons, 82.0 ± 12.6 in the NIDDM group without MA, 44.5 ± 14.3% in the NIDDM group with MA, 60.8 ± 9.2% in the IDDM group without MA, 35.0 ± 8.7% in the IDDM group with MA, and 44.7 ± 14.3% in the PaDM group. The PABA recovery was significantly lower in the IDDM group than in the group of healthy persons ($P < 0.001$). On the other hand, in the NIDDM group, the PABA recovery was significantly lower in the group with MA than in the group of healthy persons ($P < 0.001$), but was about the same in both the group without MA and the group of healthy persons. In the group without MA, the PABA recovery was significantly lower in the IDDM group than in the NIDDM group, while the group with MA showed depressed PABA recovery similar to that of the PaDM group.

Figure 2 shows the hourly cumulative urinary excretion of PABA in the group of healthy persons and in the IDDM and NIDDM groups without MA. As is clear from this figure, the group of healthy persons and NIDDM group without MA showed a similar tendency. The IDDM group without MA showed obviously depressed cumulative urinary excretion of PABA as early as at two hours, as compared to the mean level in healthy persons.

Figure 3 diagrams the relationship between PFD test results and pancreatic B cell function in healthy persons and patients with primary diabetes mellitus. Apart from the group of diabetics with MA, there is a significant correlation ($N = 32$, $r = 0.626$, $P < 0.001$) between PFD test results and pancreatic B cell function, whereas there is no correlation in the group with MA.

To clarify diminished pancreatic exocrine func-

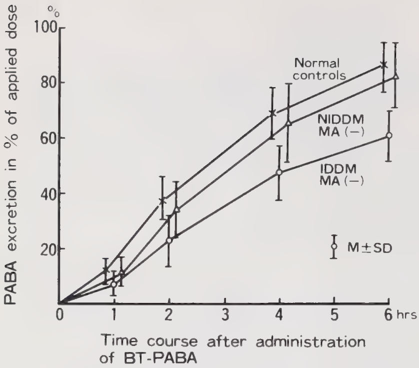

FIG. 2. Time course of cumulative urinary PABA excretion

tion in groups with MA, the PABA absorption test was also performed in some patients. The clinical picture and PFD test and PABA absorption test results in 6 IDDM patients are shown in Table II. Cases 4, 5, and 6 were with MA, having remarkably small values of CV and marked autonomic neuropathy. They frequently had diarrhea. The PABA recovery was depressed in all the six IDDM patients, especially in the patients with MA. The PABA absorption test revealed that PABA absorption was disturbed in the patients with MA, judging from their value compared against 96.4% in healthy persons. The PFD/PABA test result ratio hardly differed from the group with MA to the one without MA.

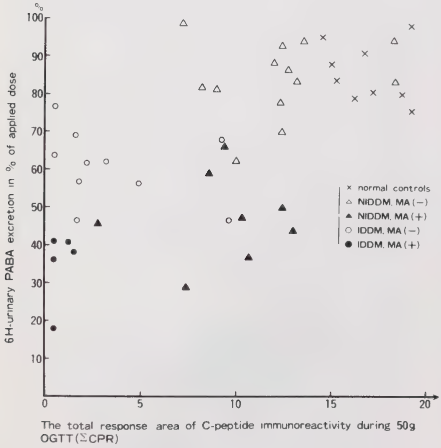

FIG. 3. The relationship between PFD test and pancreatic B cell function

Figure 4 shows the results of PFD tests which were performed in the same patients during the time their blood glucose was poorly controlled and during the time it was well controlled. The symbol ◉ indicates the patients in whom the PFD test results could be completed between the time their blood glucose was so poorly controlled that they had ketosis and the time their blood glucose was well controlled by insulin therapy. In these patients, the PFD test results showed a clear improvement after insulin therapy, but it appeared that the PFD test results were not affected appreciably by the state of blood glucose control except in such extreme cases.

Discussion

BT-PABA which is administered orally is easily hydrolyzed in the duodenum by chymotrypsin contained in pancreatic juice, liberating PABA. The enzymatic activity of chymotrypsin in the duodenum is greatly affected by the internal conditions of the duodenum, such as pH and amount of pancreatic juice. In this respect, the PFD can be said to represent a comprehensive pancreatic exocrine function test.

When pancreatic exocrine function in diabetics was determined by the PFD test, it was revealed that pancreatic exocrine function varied with the type and stage of diabetes mellitus.

Almost all IDDM patients showed depressed PABA excretion in the PFD test. It was reported by Frier et al (2) that pancreatic exocrine function was diminished in IDDM patients. They performed the P-S test in 18 insulin-dependent patients with juvenile-onset diabetes mellitus and found that there was a close correlation between the bicarbonate concentration and amylase activity in pancreatic juice and residual pancreatic B cell function. It was also observed in our study that every patient with depressed ΣCPR also showed depressed PABA excretion in the PFD test. Diminished PABA excretion in the PFD test was already noted in IDDM patients with a short length of history who had not developed diabetic microangiopathy yet. It is still a matter of debate whether diminished pancreatic exocrine function results mainly from diminished residual pancreatic B cell function. In recent years much work has been done in the studies on the vascular system of the pancreas and the postulate is made that there exists an "insuloacinar portal system" between the islets of Langerhans and the

TABLE II

Clinical picture of 6 IDDM patients and their PFD test, PABA absorption test

Patient No.	Age	Sex	Duration of Diabetes (years)	Type of insulin	Insulin dose (U)	Retinopathy (Scott's classification)	CV of R-R interval on ECG
1	23	♀	0	Lente	12	(−)	5.0
2	16	♀	5	Actrapid Lente	12 28	Ia	6.0
3	33	♂	9	Actrapid Lente	16 28	Ia	3.1
4	31	♂	10	Actrapid Lente	12 56	IIIb	1.6
5	26	♂	15	Lente	40	IV	0.9
6	31	♂	11	Lente	24	IV	0.7

TABLE II—*Continued*

Patient No.	Age	Sex	Diarrhea	BT-PABA (%) (PFD test)	PABA absorption test (%)	BT-PABA/PABA	$\sum$CPR
1	23	♀	−	67.7	99.8	0.68	8.3
2	16	♀	−	46.0	86.6	0.53	1.6
3	33	♂	−	56.5	94.0	0.60	1.8
4	31	♂	+	41.9	73.7	0.57	<1.2
5	26	♂	+	35.7	71.0	0.50	<1.2
6	31	♂	+	38.0	70.2	0.54	1.6

pancreatic exocrine tissue and that the pancreatic exocrine tissue is under the influence of high concentrations of pancreatic islet hormones (7). Further, much information has been accumulated concerning the pancreatic exocrine-endocrine relationship. Unger and Söling had the view that insulin has a trophic effect on the pancreatic acinar cell and plays an important role in the synthesis of amylase, but is not associated with the synthesis of trypsinogen and chymotrypsinogen (8). Accordingly, it is necessary to consider factors other than diminished residual pancreatic B cell function to explain depressed PABA excretion in the PFD test in IDDM patients. It has been revealed by autopsies that the pancreas are reduced in size in IDDM patients. Doniach et al found that not only was the number of islets of Langerhans reduced, but the weight of the pancreas was reduced and the pancreatic exocrine tissue showed fibrosis in IDDM patients on autopsy (9). Recently viral infection has been attracting attention as a possible cause of IDDM. It was disclosed in one case report autopsied shortly after onset of IDDM that not only the islets of Langerhans but also the pancreatic exocrine tissue was affected with virus (10). It is therefore necessary to consider that pancreatic exocrine function in IDDM patients can be disturbed in such ways.

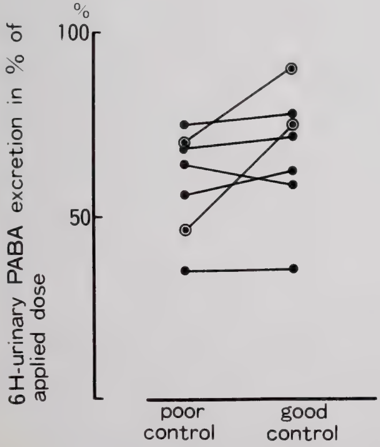

FIG. 4. The comparison of the PFD test between poor control and good control of blood glucose in the same patient.

In patients with a long length of history of IDDM complicated by microangiopathy and autonomic neuropathy, the PFD values were further depressed. This was thought mainly due to the diminished absorption of PABA from the intestinal tract. It is of interest to note that all such IDDM patients frequently had indolent diarrhea.

Diabetic diarrhea had been attributed to diabetic autonomic neuropathy (11). In the present study, it was disclosed that diarrhea occurred with high frequency in diabetics with both diminished pancreatic exocrine function and marked autonomic neuropathy. This suggests that diminished pancreatic exocrine function need be taken into consideration when finding the cause of diabetic diarrhea.

The PFD test yielded low values in NIDDM patients too, when they had a long length of history of disease and such complications as microangiopathy and autonomic neuropathy. The problem of PABA absorption need to be considered in this connection, but it is also necessary to consider diminished pancreatic exocrine function which is attributable to pancreatic vascular disorders arising from arteriosclerotic changes or fat infiltration to the pancreas. It has been reported that the atrophy and fibrosis of pancreatic exocrine tissue is seen with high frequency in autopsied cases of a long length of history of diabetes mellitus complicated by marked microangiopathy (12). These findings and reports suggest that diminished pancreatic exocrine function should be taken into consideration without fail when NIDDM patients are observed for extended periods.

Conclusion

Pancreatic exocrine function was determined in patients with diabetes mellitus by PFD test, a simple but reliable pancreatic exocrine function test, and it was revealed that pancreatic exocrine function was clearly diminished in patients with insulin-dependent diabetes mellitus. The PFD test also yielded low values in patients with noninsulin-dependent diabetes mellitus, when they had a long length of history of disease and complications.

Taken altogether, it appears that the pancreatic exocrine function test furnishes information of value to the pathological and physiologic studies of diabetes mellitus as well as to the long term management and treatment of the disease.

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The Value of the Tanner #19 Procedure in Postoperative Bilious Vomiting with Efferent Loop Obstruction

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Abstract

Efferent loop obstruction with a long afferent loop may be successfully treated using the Tanner #19 en-Y method, which is technically simple and effective in relieving the obstruction and preventing subsequent reflux.

When the afferent loop is short and cannot be mobilized, a Braun duodenojejunostomy is occasionally of value.

The chronic afferent loop syndrome is a well recognized sequel to gastroenterostomy. It usually results from obstruction of a long afferent loop. It was originally described in Great Britain by Mimpriss in 1948 (1), and its pathogenesis and clinical picture were defined by Wells, and Welbourn, and Capper in the early 1950's (2–4). A similar type of incomplete and recurrent obstruction can also affect the efferent loop. In both afferent and efferent loop obstruction, the origin of the problem is mechanical—a kink, a twist, a retroanastomotic hernia, or an area of constriction as by the transverse mesocolon.

In this paper, we describe the case histories of three patients with primarily efferent loop obstruction, secondary afferent loop stasis and varying degrees of jejunogastric reflux with bile gastritis. Vomiting of a mixture of food and bile was a feature of all three patients, and extreme weight loss and debility occurred in the two elderly patients.

Case Reports

Case #1 V.A.: The first patient was a 72-year-old female transferred to this hospital with an eight-month history of gastrointestinal dysfunction. In June of 1975, she underwent a vagotomy and pyloroplasty for a bleeding duodenal ulcer. Postoperatively, she developed gastric outlet obstruction, which eventually led to reoperation approximately six months later with the creation of a gastroenterostomy. Following the second procedure, she developed severe postprandial epigastric fullness associated with, and followed by, bilious vomiting. She deteriorated systematically over the next two months during which time she lost over 30 pounds in weight. She remained bedridden. Upper gastrointestinal series revealed that the stomach emptied through the pyloroplasty quite adequately but that the gastrointestinal contents appeared to reflux back into the stomach when reaching the gastroenterostomy, suggesting some degree of efferent loop obstruction. This was followed by vomiting of bile, or a mixture of food and bile. Upper gastrointestinal endoscopy revealed the gastroenterostomy opening but visualized only one patent anastomotic limb. This limb was entered and the scope advanced until it re-entered the stomach in retrograde manner, proving the patency of the afferent loop. X-ray revealed a rather long afferent loop. She was given an eight-week course of hyperalimentation to improve her nutritional status. She underwent a Tanner #19 procedure with transection of the afferent loop and reanastomosis of the proximal and distal limbs into the afferent loop distal to the site of obstruction

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(Fig. 1, Top). Within two weeks of surgery, she was eating a normal diet and rapidly regained all the previously lost weight over the next few months. She subsequently developed a fracture of her left hip, a result of longstanding osteoporosis, which required insertion of a prosthesis.

Case #2 S.M.: A 35-year-old female patient was admitted to this hospital with a history of epigastric pain. A GI series revealed a moderately sized hiatus hernia with reflux, and gastroscopy demonstrated antral gastritis with a 1 cm gastric ulcer. Following failure to respond to adequate medical treatment, an antecolic Billroth II hemigastrectomy and a Hill type hiatal hernia repair was carried out. She developed severe postprandial epigastric pain relieved somewhat by vomiting of a mixture of food and bile. She also developed moderate watery diarrhea. A barium meal revealed a long afferent loop which filled immediately after dye entered the stomach with passage of dye to the duodenal bulb. Thereafter, the stomach slowly filled and eventually the food passed slowly through into the efferent loop and into the small bowel (Fig. 2).

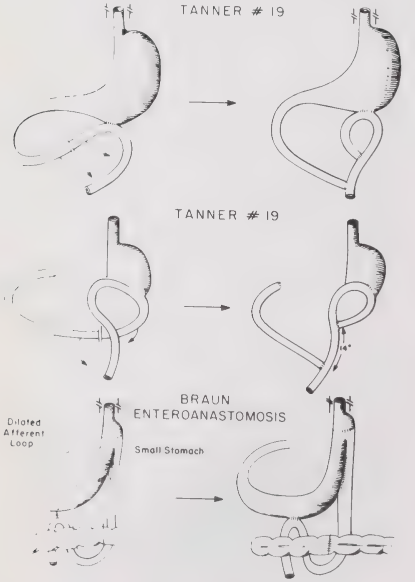

FIG. 1. Diagrammatic representation of preoperative and postoperative anatomical configuration in cases 1–3. A Tanner #19 operation was done in cases #1 and #2, and a Braun duodeno-jejunostomy in case #3.

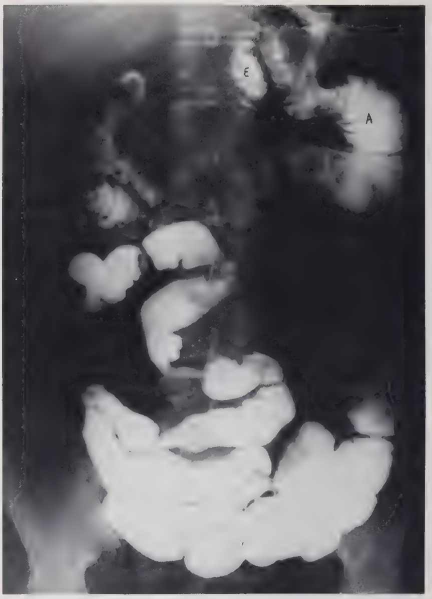

FIG. 2. Upper gastrointestinal series on patient #2 which showed immediate filling of exceedingly long afferent loop (A) at fluoroscopy with spill over into efferent loop (E), and considerable delay in emptying of afferent loop.

At reexploration, the efferent loop was adherent anteriorly to the overlying wound, and the stomach and afferent loop were filled with bile, food, and mucous indicative of stasis and outlet obstruction. As the food passed preferentially into the afferent loop we decided to maintain this primary route of egress from the stomach and carried out a Roux-en-Y Tanner procedure. Postoperatively, the vomiting of bile and food, and the diarrhea (probably secondary to bacterial overgrowth) have ceased. She still complains of some dysphagia related to a slight narrowing of the distal esophagus at the site of the hiatus hernia repair.

Case #3 M.A.: This was a 73-year-old lady admitted with a previous history of six operative procedures, three of which were upon the stomach. Three of her previous operations were a cholecystectomy, a hysterectomy, and a total left hip replacement. The gastric operative procedures carried out over the previous five years were a vagotomy, as pyloroplasty, and a subsequent gastrectomy for perforated and obstructing duodenal ulceration. Following this, she developed recurrent bleeding and a 90% gastric resection was carried out.

During the months prior to this admission, she had lost 40 pounds in weight and had become completely bed-ridden. She complained severely of violent, bilious vomiting following each meal. She experienced severe right upper quadrant abdominal pain associated with visible peristalsis. Examination revealed a debilitated elderly lady with evidence of considerable weight loss and dehydration. Upper gastrointestinal series showed rapid passage of the barium into a markedly dilated afferent loop, with slow subsequent spillover into the efferent loop and jejunum (Fig. 3). UGI endoscopy revealed a large afferent limb, and an obstructed efferent limb that could not be entered with the endoscope. Intravenous hyperalimentation was instituted for a period of two weeks during which time she regained ten pounds in weight, and was in a considerably improved physical condition when taken to surgery.

At surgery, she was noted to have multiple adhesions from the previous operative procedures. There was a very small gastric remnant with a retrocolic anastomosis. The gastroenterostomy was rotated so that the markedly dilated afferent loop lay anterior to, and intimately adherent to the collapsed, obstructed, efferent loop (Figs. 1, 3). The transverse duodenum increased to approximately 5 cms in diameter (Fig. 3). In addition, a loop of jejunum had herniated through the right transverse mesocolon, and was lying adjacent to the afferent loop as seen in the Figure 1 (Case 3). During the course of dissection, it was necessary to ligate the marginal artery to separate the colon from the underlying loops and this resulted in compromise of a small segment of colon, which was resected and reanastomosed by colocolostomy. It was impossible to free the afferent and efferent loops from the pancreas and ultimately a side-to-side duodenojejunostomy was carried out. She did well postoperatively and left the hospital pain-free, although debilitated by chronic arthritis.

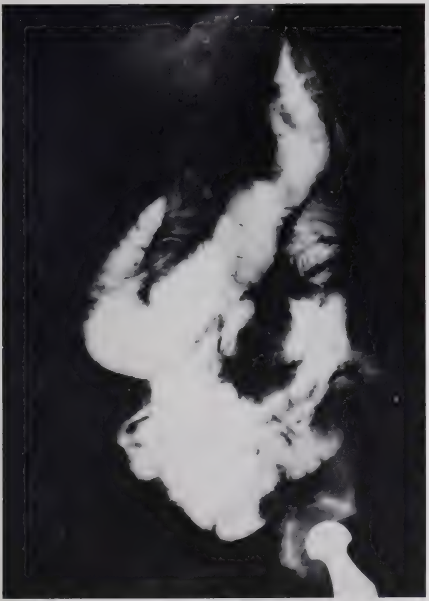

FIG. 3. Upper gastrointestinal series on patient #3 showing markedly dilated afferent loop which filled immediately with subsequent flow into posteriorly placed efferent loop.

Discussion

Postgastrectomy bilious vomiting following Billroth II (2−7) gastrectomy has been described in Europe and Scandanavia in up to 23% of patients. It is less frequent in recent years because of a progressive reduction in size of the afferent loop. Most instances are directly related to afferent loop obstruction but a small proportion are secondary to obstruction of the efferent loop. Goligher et al (8) found bilious vomiting to be more common in female patients and all three of our patients were women.

Efferent and afferent loop obstruction may be distinguished by clinical, endoscopic, and radiologic evaluation. The efferent loop syndrome is characterized by vomiting of food mixed with bile, aspiration of bile stained material directly from the stomach, and rapid filling of a dilated afferent loop. The afferent loop syndrome, by contrast, is associated with epigastric discomfort, relieved by bilious vomiting (occasionally mixed with food), and shows complete failure to fill the afferent loop with barium. An endoscope will pass preferentially into the afferent limb in the former, and the efferent limb in the latter.

The vomiting in our patients was in general nonprojectile, except perhaps in patient number three, and in each patient a relatively long afferent loop was clearly demonstrated radiologically. Following gastrectomy in patients 2 and 3, the afferent loop filled rapidly and then slowly emptied back into a partially filled stomach which was the site of stasis of bile and food. This material was finally evacuated distally in small amounts into the partially obstructed loop, and proximally by vomiting. In case 1, the reflux back into the stomach at the gastrojejunostomy resulted in gastritis, nausea and vomiting.

Menguy (9) has emphasized the poor prognosis of patients with postoperative bilious vomiting. Only 20% subside spontaneously. The other 80% required reoperation. Some operative procedures used with varying degrees of success to treat the problem include: enteroanastomosis (10), conversion to Billroth I (5, 13, 14), and a simple Roux-en-Y (15–17).

In 1964, Tanner described a technique now widely recognized as the Tanner "19" procedure in which a long afferent loop is transected and both the proximal and distal limbs reimplanted into the efferent jejunum. (Fig. 1, Cases 1 and 2). We have found the latter to be an excellent technique, simple to effect and requiring minimal dissection, particularly in patients with an antecolic anastomosis. All authors who have used the Tanner 19 procedure including Tanner (16), Herrington (19), Bartlett (20) and Welch (21), have been extremely gratified with the results. The value of this procedure derives from a) its simplicity, b) the total diversion of bile from the stomach and, c) the certainty that the stomach will empty freely from the enteroanastomosis as both afferent and efferent anastomoses are left intact. Furthermore, this simple double anastomosis may be utilized in either afferent or efferent loop obstruction. Regardless of whether the stomach empties primarily through afferent or efferent loop it will continue to empty satisfactorily following this procedure.

Conclusions

(1) The Tanner-en-Y procedure is the procedure of choice in cases of postgastrectomy afferent or efferent loop obstruction as it is simple to carry out, and the results are excellent.

(2) The double anastomosis effectively controls problems related to both bile reflux and gastric emptying.

(3) A simple Roux-en-Y diversion should probably be utilized if the afferent loop is very short so that there is insufficient length to create a second anastomosis.

(4) In the rare instance where the only accessible part of a dilated efferent loop is that adjacent to the head of pancreas, a Braun type enteroanastomosis should still be considered as it is occasionally successful.

Acknowledgment

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Cervical Thymic Cyst

MOSES NUSSBAUM, M.D., AND JONATHAN G. SARLIN, M.D.

Cervical thymic cysts, especially in a nonpediatric age group, are extremely rare lesions. Sixty-six documented cases have been reported in the literature, 43 of which have appeared in patients under the age of 20. Twenty-three appear in the older age group. Two recent publications have detailed the embryology of the thymus (1, 2).

Essential to the formation of cervical thymic deposits is the fact that thymic buds arise from the ventral portions of the third pharyngeal pouch and migrate caudally, forming a thymopharyngeal duct. The pharyngeal ends close off and the thymic masses descend to the mediastinum and fuse. It is in the course of the descent from the embryologic pharynx to the adult mediastinum that thymic cells may drop off and form rests along the course of the descent. The etiology of cyst formation within thymic rests is not clear but a number of theories exist (3).

Case Report

A 19-year-old white male was admitted to Beth Israel Medical Center on September 26, 1978. He had first noted a right neck mass in February 1978 which varied in size with upper respiratory infection, but remained asymptomatic. There was no relevant previous medical history. Review of his symptoms and family history revealed no pertinent information. He was a heavy cigarette smoker and moderate beer drinker.

Physical examination showed a well-nourished male in no distress. A right neck mass measuring approximately 3 × 3 cm was present, which on different examinations varied in the impression it gave from a large solitary mass to one that felt like multiple matted lymph nodes. Preoperative laboratory data was within normal limits. Preoperative diagnosis lay between lymphoma and a congenital cyst, probably a branchial cleft cyst.

Surgery was performed on September 27, 1978 through a transverse incision made over the presenting mass which was located at the level of the bifurcation of the common carotid artery. A 7 × 8 cm mass was excised which was cystic for the most part, with several firm areas within it. Superiorly, the mass was closely adherent to the upper portion of the internal jugular vein and the carotid artery, but was separated from these structures. Inferiorly, the mass continued down along the vagus nerve and the carotid sheath. To remove it, a second incision had to be made 6 cm below the first. At that point the lower margin of the cyst was identified and freed so that the entire mass could be delivered through the main wound. Both wounds were closed routinely and there were no postoperative complications (Fig. 1).

The patient has been well since without recurrence of the mass for one and a half years.

Pathologic Examination

The tissue was fixed in formalin, routinely processed and embedded in paraffin and stained with hematoxylin and eosin.

The surgical specimen consisted of an 8.0 × 6.5 × 3.0 cm tapered, pyriform, multiloculated cystic structure containing turbid fluid and exhibiting soft yellow foci within its firm gray solid portions. Microscopically, cysts lined by thymic epithelium were set in a fibrous stroma containing islands of thymic tissue with Hassal's corpuscles, and cholesterol granulomata. An occasional germinal center was present (Figs. 2–5).

Discussion

The increased frequency of case reports (32 cases prior to 1962, and the remainder, 34, since) testifies to the pathologist's ability to differentiate these lesions from the larger group of congenital cystic masses such as branchial cleft cysts and cystic hygromas. They are commonly found in

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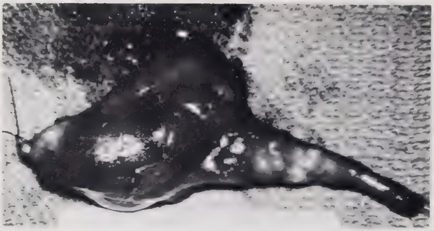

FIG. 1. Gross appearance of the surgical specimen.

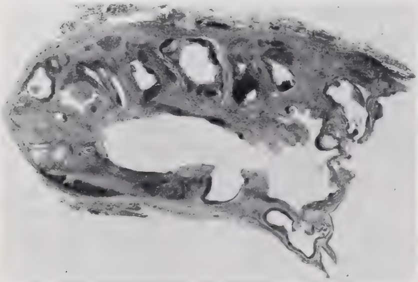

FIG. 2. A whole mount cross section of the specimen, showing its multiloculated structure (H & E, 6×).

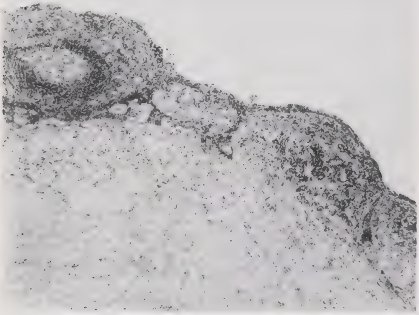

FIG. 3. Illustrating a cyst lined by thymic epithelium. A germinal center is evident (H & E, 48×).

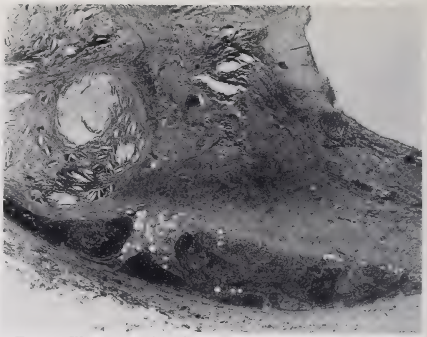

FIG. 4. Illustrates the fibrous cyst wall with thymic tissue and cholesterol granulomata (H & E, 26×).

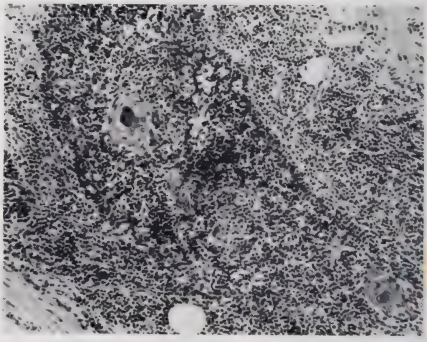

FIG. 5. Illustrates Hassal's corpuscles within an island of thymic tissue (H & E, 120×).

children, and only histologic examination of excised tissue can provide the true diagnosis. In late adolescence and early adulthood, as our case illustrates, lymphomas and thyroid carcinomas are added to the differential diagnosis. In neither the pediatric nor the adolescent age group is there any diagnostic test which can be relied upon to distinguish thymic cysts from the other possible diagnoses. Review of the published material indicates that a correct preoperative diagnosis has apparently never been made. Preoperative scanning and x-ray procedures, other than confirming a soft tissue mass with both cystic and solid elements, are of no great value. Excision of the mass must be carried out and the therapy of cervical thymic cysts therefore remains surgical.

Summary

A lateral cervical thymic cyst in a 19-year-old male is reported. Sixty-six such documented cases have appeared in the literature, most of them in the past eighteen years. The clinical and histologic differentiation of these masses from the more common branchial cleft cysts and cystic hygromas is emphasized. Successful surgical therapy is the choice in these cases.

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A New Method for Determining Serum Amlyase Inhibitor: A Possible Role in the Pathogenesis of Pancreatic Inflammation*

SERGEY A. TUZHILIN, MD, PH.D. AND DAVID A. DREILING, M.D.

In the previous papers (1–3) serum amylase inhibitor concentrations were determined by a dilution technique (2) in patient's with and without pancreatic disease. Although the data showed variability, the findings suggested a role of amylase inhibitor levels in the regulation of serum amylase activity and in the diagnosis of pancreatic disorders.

This preliminary report presents a new method of determining serum amylase inhibitor activity, a method based upon splitting of the amylase/amylase inhibitor complex by the proteolytic enzyme trypsin.

Materials and Methods

The following determinations were made on 14 patients in this study:

1. Serum amylase was estimated by the method of Smith-Roe (4)
2. Amylase activity was determined by this method in the following:
   a. whole serum
   b. serum diluted 1:2 with buffer
   c. undiluted serum incubated with crystalline trypsin (50 mg Mann Research Trypsin to 0.6 ml serum)
   d. serum diluted 1:2 and incubated with trypsin

Amylase inhibitor activity can be expressed as differences between the observed findings or as percentage increased activity obtained after dilution or incubation with trypsin.

The patients included in the study were observed in the Pancreatic Diagnostic Laboratory and comprised individuals without pancreatic disease and those with chronic but not acute pancreatic inflammation.

The normal range of serum amylase activity determined by the Smith-Roe method is 61–120 u/100 ml.

Results

Table I presents average serum amylase activity in Smith-Roe units/100 cc in whole and diluted (1:2) serum before and after incubation with trypsin. The patients are divided into two groups: 1) those with whole serum amylase levels below 48 u% and 2) those with amylase activities above 48 u%. In both groups a 1:2 buffer dilution of whole serum (lines A and D) resulted in a statistically significant increase in amylase activity. Incubation of the whole serum with trypsin (lines B and E) also statistically increased amylase activity in both groups. However, when serum diluted 1:2 was incubated with trypsin, the average amylase activity in the group with whole serum amylase concentrations below 48 u% (group 1) was increased statistically; whereas the activity of the patients with initial amylase concentrations above 48 u% (group 2) was statistically decreased.

Discussion

The data clearly demonstrates that a portion of the serum amylase is complexed with an inhibitor and that this complex can be dissociated by dilution or by incubation with trypsin. Correlary to this, is the concept that the level of serum

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TABLE I

Amylase Level in Whole and Diluted (1:2) Serum Blood Before and After Its Incubation with Trypsin

	BEFORE THE INCUBATION			AFTER THE INCUBATION			
	Whole Serum	Diluted Serum (1:2)		Whole Serum		Diluted Serum (1:2)	
	M ± SD	M ± SD	P	M ± SD	P	M ± SD	P
1. THE INITIAL LEVEL OF AMYLASE IN THE WHOLE SERUM IS BELOW THE NORM (<48 units/100 ml) (9 PATIENTS)							
A)	25 ± 14	115 ± 52	<0.001	—	—	—	—
B)	25 ± 14	—	—	65 ± 30	<0.001	—	—
C)	—	—	—	65 ± 30	—	171 ± 46	<0.001
2. THE INITIAL LEVEL OF AMYLASE IN THE WHOLE SERUM IS NORMAL OR HIGHER THAN NORM (>48 units/100 ml) (5 PATIENTS)							
D)	73 ± 25	137 ± 22	<0.02	—	—	—	—
E)	73 ± 25	—	—	117 ± 40	<0.02	—	—
F)	—	—	—	117 ± 40	—	43 ± 54	>0.10

amylase activity depends not only upon the delivery of this enzyme to the blood from the pancreas but also the rate of entry of amylase inhibitor. Further, increased serum amylase activity could result from increased entry of the enzyme as well as decreased release of inhibitor. Finally, low serum amylase activity could follow increased inhibitor entry into the serum.

In the past, amylase inhibitor activity has been calculated as the percentage increased activity obtained after dilution of whole serum 1:2 or incubation of whole serum with trypsin. It can also be defined as the difference in amylase activity between diluted serum and whole serum (DAI) or as the difference in amylase activity between trypsin incubated serum and whole serum (TAI). Finally, amylase inhibitor activity theoretically can be expressed as the difference between the amylase activity of the whole undiluted serum and/or the most active amylase value of one of the following: the diluted serum, the serum incubated with trypsin or the diluted serum incubated with trypsin.

On this basis, group 1 patients, that is, those with whole serum amylase activity below 48 u/100 ml, had an average amylase inhibitor activity of 146 u/100 ml, while group 2 patients, those with whole serum amylase activity greater than 48 u/100 ml had an inhibitor activity of 63 u/100 ml. Thus, the low serum amylase activity in group 1 can be partially due to high inhibitor concentrations. Moreover, in this group, splitting of the amylase-inhibitor complex required both dilution and trypsin digestion. On the other hand, the higher standard serum amylase activity in group 2 patients appears to be a result of lower amylase inhibitor concentration. In these patients, moreover, dilution of the whole serum appears to be sufficient to split the amylase-inhibitor complex. Finally, incubation of the diluted serum with trypsin, not only fails to release additional amylase activity but also apparently causes amylase activity loss presumably by tryptic digestion.

This interesting phenomenon requires study in patients with acute chronic pancreatic disease.

Conclusions

1. In serum, amylase exists in free active form and is bound with an amylase inhibitor.
2. Dilution of whole serum or incubation with a proteolytic enzyme such as trypsin dissociates the complexed amylase and increases measured amylase activity.
3. A method of determining amylase inhibitor activity is proposed.
4. Low serum amylase activity is frequently associated with high inhibitor activity and visa versa.

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Structure of the Major Duodenal Papilla

Carlos Velasco Suarez, M.D.

Introduction

Obstructive choledocholithiasis may be complicated by cholangitis, liver abscess(es) or pancreatitis resulting in high morbidity and mortality. The duodenal ampulla and the existence of a common channel, formed by the confluence of the choledochus and pancreatic duct, are of major importance in the pathogenesis of these complications.

The studies reported here deal with the anatomy of the distal choledochus, the major duodenal papilla of Vater, and the periampullary region.

Materials and Methods

Postmortem specimens of the duodenopancreatic regions were obtained from 150 cadavers. The specimens contained the entire duodenum and pancreas including the first jejunal loop and extending to the hilus of the liver and spleen.

Gross architecture was studied in 142 and histologic morphology in eight specimens.

Macroscopic Studies

The specimens were photographed before and after dissection aimed at separation of the biliary system from the duodenum and pancreas; the latter was transected at the level of the pancreatic neck or body. Dissections were performed with special scalpels since the corrosion method proved destructive to the tissues.

Photographs were taken after opening the duodenum and after cannulation of the biliary and pancreatic ducts. Later, the studies commenced with contrast radiography of the pancreatic and biliary ducts after ligation of the pylorus and jejunum.

Pancreatic dissections began with separation of the ventral from the dorsal segments containing the ducts of Wirsung and Santorini, respectively. A plane between the two ducts exists with two or more cm of the duct of Wirsung which can be easily ligated away from the duodenum, thus permitting a partial ventral pancreatectomy. Unlike the easy extraduodenal dissection of Wirsung's duct, the duct of Santorini cannot be isolated and ligated outside the duodenum. The duct of Santorini is surrounded by pancreatic tissue throughout its course down to its insertion in the duodenal mucosa. Here, the wide separation of the longitudinal, and to a lesser degree the circular, muscle layers of the duodenum define the obliquity in the insertion of Santorini's duct.

In only two instances was the duct of Santorini the only or dominant excretory pathway. Variable interconnection between the two ducts existed in most cases, but this interconnection was absent in few. Fibrous obliteration of the duct of Santorini within the duodenal submucosa was found in a small number of cases. Rarely, one or two supernummerary ducts overlying the dorsal pancreas were observed.

The pancreatic duct entries into the duodenum were predominantly filiform, whereas a slight ampulla formation was seen in a few cases. However, ampullary dilatation was less prominent than formation of a common channel.

The *caruncles* were identified and found to be consistent with the classical descriptions by Letulle and Larrier (1), and by Belou (2). A visible Santorini papilla becomes evident after catheterization. Conversely, the major duodenal papilla was always present, even in the absence of Wirsung's duct. In many instances, the two "membranes" described by Vesalius and representing well developed Santorini valves were observed.

The *frenulum* described by Santorini and varying in length from very short to several cm long was found in nearly every case and was adherent to the duodenum, thus forming the limit of a short falciform membrane. It should be easily identified, especially in the fresh specimen with un-

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fixed duodenal mucosa. The anatomic and physiologic significance of the frenulum is unclear, even though Santorini ascribed a valve function to it.

Pancreaticobiliary Dissections

Cholangiopancreatography and photography were carried out in 91 instances, follwed by formalin fixation for better tissue preservation and subsequent dissection. Representative anatomic and radiographic correlations are shown in Figures 1 and 2.

The length of the intrapapillary segment of the two ducts was variable, with complete separation in 59 and confluence in 40 percent. Ampulla formation and crossing between the main pancreatic and biliary ducts were seen in five and seven percent, respectively. These observations indicate that biliopancreatic reflux is limited to 36 percent of the cases.

In 39 cases with confluence of the two ducts, the length of the common channel was 1–3 mm in 22, 4–5 mm in 10, and 9–12 mm in 7. The common channel is thus unlikely to be greater than 10 mm and formation of an ampulla is not always present.

Valves of Santorini

These valves described by Vesalius and thoroughly studied by Santorini are two small membranes suspended loosely in the biliary ostium. We have identified them in our dissections and found them to be prominent in cases in which the choledochal ampulla was well developed. These valves are located near Wirsung's outlet, and rarely near the choledochal outlet. Santorini ascribed an antireflux function to these valves.

Duodenal Mucosal Folds

Transverse mucosal folds or valvulae conniventes are found near the major duodenal papilla. The extreme mobility of these mucosal and submucosal folds overlying the circular fibers is important in the physiology and pathophysiology of this region.

Dissection of Muscle Layers

Dissections in formalin-fixed specimens began by approaching the dorsal aspect after freeing the choledochus from the pancreas down to its penetration into the abdominal wall.

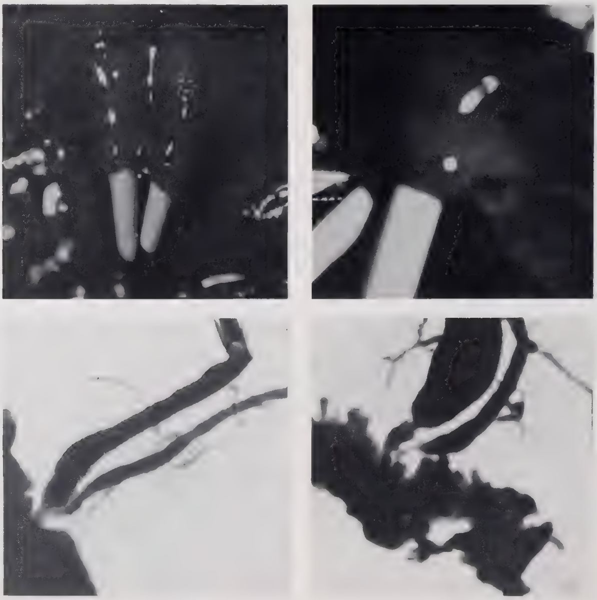

FIG. 1. Separation of the major pancreatic and bile ducts in anatomic and contrast radiographic studies.

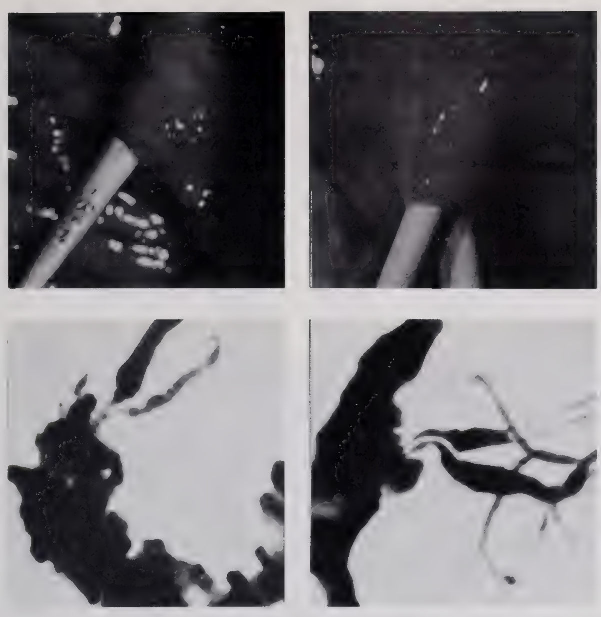

FIG. 2. Anatomic and radiographic contrast studies showing common channel and complete separation of the choledochus and pancreatic duct.

Very fine membranes covering the longitudinal muscle fibers are removed; at this point, the characteristics of the hiatus become apparent. The deeper circular muscle fibers can then be seen as they terminate in the upper margin of the duodenal "window."

Separation of the pancreas from the duodenal wall is then achieved by downward dissection. The duct of Wirsung can be isolated completely. Upward dissection exposes the dorsal pancreas and the duct of Santorini which is always surrounded by parenchyma and is in direct contact with the duodenal submucosa at a site totally devoid of duodenal muscle fibers.

Dissection around the hiatus and the duodenal "window" is continued while examining the duodenal muscle layers. Very soon, the confluent circular bundles of the choledochal sphincter are exposed. The use of carmine dye, which is avidly absorbed by the muscle fibers, facilitates identification of structures in this region.

The two margins and angles defining the duodenal "window" can be easily isolated and the connecting and reinforcing fibers of Boyden identified (3).

In the area of Wirsung's duct, it is always possible to follow the longitudinal bundles as they travel upwards and penetrate the pancreas where they become fixed.

After exposure of the two ducts, as they penetrate the duodenal wall, dissection continues along the longitudinal fibers which extend toward the submucosa surrounding the biliary outlet. These bundles of fibers run obliquely and sometimes they cross.

After reaching the submucosa surrounding the posterior wall of the choledochus or the ampulla, if it exists, the latter is opened longitudinally to study the features inside the duct.

Anterior Mucosal Dissection

Dissection of the papilla begins by removing a square piece of mucosa to expose the circular muscle fibers of the duodenum. Downward dissection is continued until all mucosa is removed down to the inferior frame of the "window" and insertion of the frenulum.

Below the submucosa, a delicate membrane separates the longitudinal muscle layer and is perforated by small blood vessels at various sites. Dissection is continued along the mucosal aspect down to the third portion of the duodenum. In the angles of the "window," the connecting and reinforcing fibers, which become horizontal, can be dissected.

After removal of the longitudinal fibers, the entire layer of circular fibers is exposed. Bands of circular fibers of uniform thickness extend from above the upper border to below the lower border of the duodenal window.

After sectioning the circular muscle layer through a vertical medial incision, the terminal choledochus and Wirsung's duct with their union become apparent. The circular bundles of the choledochal sphincter above its union with Wirsung's duct can be identified by further dissection; these choledochal sphincter fibers may vary in extent and may cover an area as long as 10 mm.

Downward dissection of the papilla proper is difficult, but it is possible to identify the interlacing oblique bundles which constitute the superficial layer of the ampulla described by Boyden. At this stage, deflection of the duodenal mucosa permits identification of the crossed or direct longitudinal bundles which are fixed to the submucosa. Finally, the entire duct is opened to examine the inner surface of the papilla or the ampulla, if one is present.

Histologic Studies

Using Mallory's trichrome and hematoxylin-eosin stains, 1703 histologic slides were made and numerous photomicrographs were studied. In most instances, the two ducts followed a separate course up to the biliary ostium; a 4 mm ampulla was found once, a union at the ostium without ampulla once, and a common channel or small ampulla once.

Studies of transverse and sagittal sections confirmed and augmented the presence of semicircular, fan-like and longitudinal fibers. The identification of these fibers permits a more precise interpretation of the physiology of this region.

Structure and Function of the Papilla

The description of muscular bundles in our work does not differ from the reports of previous investigators such as Oddi, Boyden, etc. However, the fundamental difference is the interpretation of their function and their role in pathophysiology.

Most modern investigators have ignored the old descriptions of the physiology of this area, especially the highly knowledgeable essays by Giovanni Domenico Santorini (4). It may be justified to name the pancreaticoduodenal area after Santorini. A number of anatomic peculiarities still remain inadequately explained: the extraordinary motility of the mucosa and submucosa, the presence of numerous Kerckring's folds, the phrenulum, the numerous nerve cells described by Letulle and the muscle bundles of the papilla. Furthermore, the striking structural similarity between the salivary glands and the pancreas is of great interest. All sectional functions are eventually integrated to generate a meaningful response.

Among the bifurcating bundles of muscle, there are numerous racemose glands which we have designated as retractile and dilating muscle of the papilla. They may be the release site of one or more hormones.

Contraction of the Choledochal Sphincter

Since 1936, I have held the view that the interruption of biliary flow by magnesium sulfate was due to contraction of the choledochal sphincter. The continued flow of pancreatic juice during contraction of the choledochal sphincter implied that a pancreatic duct sphincter did not exist.

Absence of Pancreatic Sphincter

After many years of studies, I have concluded that no sphincter exists in the terminal pancreatic duct, whether it enters the duodenum separately or forms a common channel or an ampulla with the bile duct.

The semicircular fibers—which become longitudinal—considered by others to form the pancreatic sphincter provoke opening rather than closure of the duct upon contraction.

The same arcuate fibers are found in Boyden's illustrations. However, Boyden (3) has stated repeatedly that "a pancreatic sphincter is rarely present and when it exists it is composed of a few weak muscular fibers."

In my studies, I have never observed a muscular ring completely surrounding any portion of the pancreatic duct. The muscle fibers described by Boyden, by Negri and others are semicircular and are found in the external part of the duct only. I have shown that these fibers become longitudinal above the biliary ostium and that they cross similar fibers of the opposite side all along the ampulla, if one exists, or the papilla, according to Boyden's concept in cases of a common channel. The intercrossing of fibers can be clearly seen in all of Boyden's illustrations (Fig. 3).

Absence of "Sphincters" of Ampulla, Papilla and Biliary Ostium

Boyden (3) and others refer to ampullary or papillar sphincters as circular bundles situated near or at the biliary ostium. This misconception has been perpetuated in a more recent report by Ivy and Gibbs (5) in which a thick and complete ring of muscle fibers is depicted in the terminal portion. This would explain the biliopancreatic reflux through simply a spasm of the alleged sphincter.

Histologic sections confirm that in this area the oblique intercrossing fibers become longitudinal and the semicircular or fan-like fibers form part of the longitudinal fiber system that ends in the posterior or anterior bundles.

The function of these fibers is to provide the opening for the bile duct, ampulla or common channel at the duodenal "window." All these dilating fibers form the papilla dilator muscle of Schreiber (6).

Papilla Retracting Muscle

Sturdy bundles of muscle fibers, especially evident on sagittal sections, begin at the angles of both margins of the duodenal "window" and run

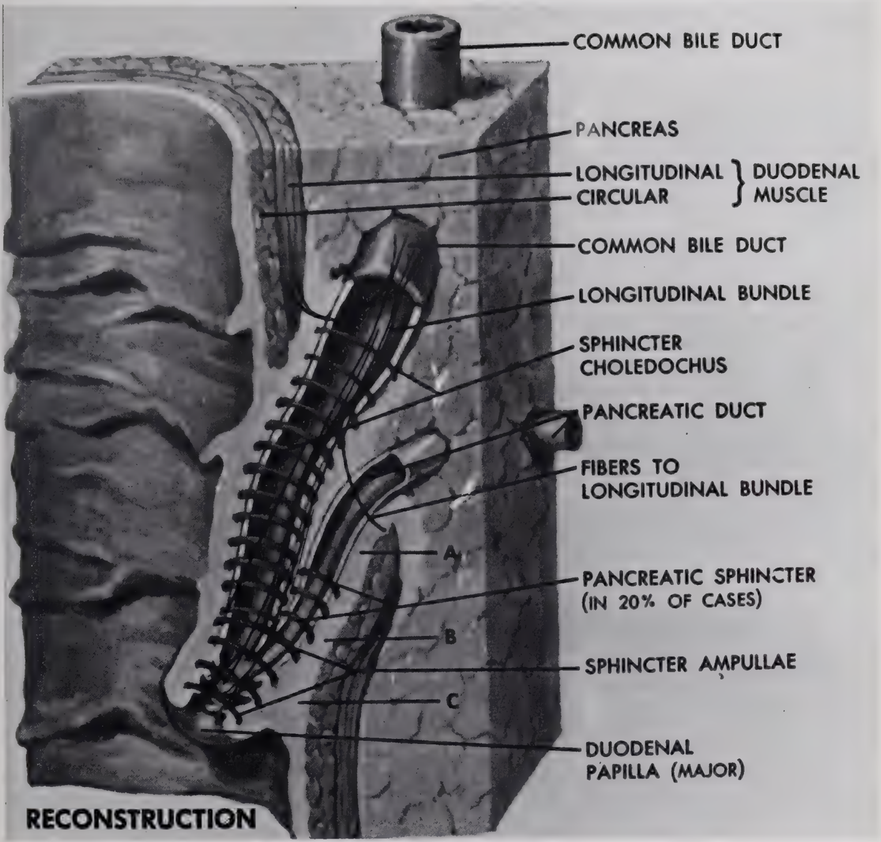
COMMON BILE DUCT
PANCREAS
LONGITUDINAL
CIRCULAR
DUODENAL MUSCLE
COMMON BILE DUCT
LONGITUDINAL BUNDLE
SPHINCTER CHOLEDOCHUS
PANCREATIC DUCT
FIBERS TO LONGITUDINAL BUNDLE
A
PANCREATIC SPHINCTER (IN 20% OF CASES)
B
SPHINCTER AMPULLAE
C
DUODENAL PAPILLA (MAJOR)
RECONSTRUCTION

FIG. 3. Diagrammatic sketch of different sphincters in the major duodenal papilla, according to Boyden. Longitudinal bundles are not shown.

upwards into the fibroconnective partitions of the pancreas. These important fibers are part of the system interconnecting the duodenal musculature with the layers of the papilla proper.

In contrast to Boyden's view, I regard these fibers as anatomically connecting and functionally complementing the action of the longitudinal fibers. The principal function of these fibers is to lift the region of the papilla and shorten the common bile duct. I have named this system the retracting muscle of the major papilla.

I have frequently observed the accordion-like shortening of the choledochus above the duodenal "window" brought on by the contraction of these fibers. This lifting and shortening of the papilla during evacuation of contrast medium from the common bile duct into the duodenum is seen on fluoroscopic image intensifiers.

Choledochal Sphincter

In gross dissections and in histologic studies, we have always found sturdy bundles of muscle fibers surrounding the terminal choledochus before its pentration into the duodenal "window" and extending down to the junction with the pancreatic duct, if such union exists. When an ampulla or common channel exist, the bundles of muscle fibers continue down to the opening into the duodenum.

I do not agree with Boyden's subdivision into an upper and lower choledochal sphincter; this arbitrary separation may be confusing. In reality, there is only one choledochal sphincter which comprises all the fibers assigned to the two sphincters by Boyden.

The function of this sphincter is to control bile flow and facilitate storage of bile in the gallbladder during fasting.

Bile flow into the duodenum results from contraction of the gallbladder and from the action of the retracting and dilating muscle of the papilla which retracts the bile duct and keeps it patent during bile flow. The same mechanism of the retracting and dilating muscles of the papilla facilitates the flow of pancreatic juice which has a lower viscosity than bile and flows under greater secretory pressure.

The Role of Duodenal Musculature

Participation of the duodènal muscles in bile flow has been controversial. Oddi et al (7) ascribed to it a significant or dominant role, whereas Boyden and we have considered the choledochal sphincter as an essential organ that regulates bile flow.

Colp and Doubilet (8) may be mistaken in attributing the lifting of the papilla and closure of the two ducts to the circular duodenal muscle by compression of the intramural area. Their finding of persistence of high biliary pressures after sphincterotomy is due to incomplete sectioning of the sphincter, up to 8 mm from the biliary ostium. We have found well developed choledochal sphincter fibers well above the level of 8 mm.

Retrograde Filling of Wirsung's Duct at Cholangiography

Partial filling of Wirsung's duct during cholangiography is another argument advanced by those who support the existence of sphincters in the ampulla or the papillary opening. The generally accepted explanation is that retrograde filling of the pancreatic duct is due to a spasm of the papillary sphincter or Boyden's ampullary sphincter, if the union of the two ducts occurs above the ampulla.

My observations lead me to believe that the reflux is due to a combination of various causes:

a) Anatomic: the reflux is seen in patients with union of the ducts above the biliary orifice.
b) Mechanical: the reflux can be avoided, if the contrast medium is allowed to flow by gravity from a level not greater than 30 cm from the abdominal wall, rather than being injected by manual pressure.

I have thus established that the reflux was not due to resistance of a sphincter but due to distension of the ampulla, if it exists, or of a common channel. I have, therefore, concluded that pancreatic duct reflux during cholangiography is due to spasm of the choledochal sphincter and that no sphincters exist at the biliary orifice.

U-Shaped, Longitudinal, Semicircular, and Interlacing Fibers

The retracting and dilating muscle that I have described displays certain analogies to the rectal sphincter mechanism. The rectal ampulla, like the terminal choledochus, ends in a narrow segment and changes direction to wind the anorectal canal, which forms a 90° angle with the rectal ampulla. Furthermore, the longitudinal and circular fibers of the rectal ampulla behave almost exactly as those in the terminal choledochus, as described by me. The longitudinal fibers of the rectum form an anterior and a posterior bundle as they descend toward the terminal portion of the ampulla, then change direction to become semicircular, interlacing with similar fibers from the opposite side. The circular bundles form the powerful internal sphincter of the rectum (Fig. 4).

The longitudinal bundles of the rectum divide into several layers, one of which ends below the aponeurosis of the levator and forms a mixed system of U-shaped fibers. Laimen (9) described this curious arrangement in a very complete study. Thus, the longitudinal fibers of the choledochus which become semicircular facilitate evacuation by shortening and dilating the terminal portion of a duct.

Conclusions

In the terminal portion of the choledochus, there exists only one sphincter constituted by bundles of arciform or semicircular fibers which surround the duct in its entirety. These fibers commence before the duct passes through the duodenal "window" and extend downwards an average distance of some 5–10 mm.

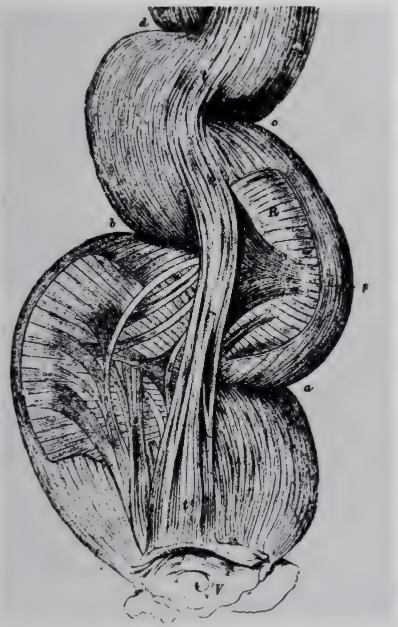

Fig. 4. Muscle fibers of the rectal ampulla. U-shaped and intercrossing fibers changing from longitudinal to horizontal and semicircular (Reference 8).

In fact, there does not exist a ring-shaped sphincter. The bundles always constitute arciform or semicircular structures and nearly always arise from the areas within the two large longitudinal bundles with which many of these fibers are connected. In reality this arrangement represents, in adults, the two "half-cylinders" described by Schwegler and Boyden in fetuses (9).

In the terminal portion of the choledochus or in the common channel or the ampulla when such exists, the bundles follow an oblique direction and become intercrossed as can be appreciated in the illustrations provided by all the authors, from Hendrickson to Dardinsky, Boyden, and Schreiber. The mission of the half-moon-shaped fibers described by Oddi, which are always observed in the orifice of the papilla at one side of Wirsung's duct and which continue upwards with longitudinal fibers ending in two bundles, is to open the biliary ostium and the terminal portion of the papilla. This function takes place together with the contraction of the two longitudinal bundles and the semicircular oblique fibers observed in the ampullary portion. I believe this complex constitutes the retracting and dilating muscle of the papilla.

The so-called sphincters of the ampulla, of the papilla or papillary orifice, and of the pancreatic duct, are nonexistent.

Acknowledgments

Many thanks to Dr. Demetrius Pertsemlides for having condensed my thesis to the present form for publication.

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Sclerosing Cholangitis of the Bifurcation of the Common Hepatic Duct

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Introduction

Stenosis of the bifurcation of the common hepatic duct is usually caused by primary carcinomas arising in the wall of the duct or by neoplastic invasion of the hilar lymph nodes (12). Stenosis can also be caused by sclerosing cholangitis. This disease, however, involves diffusely the extrahepatic or intrahepatic biliary tree and is very rarely localized in a segment of it (11). Both biliary tree neoplasms and sclerosing cholangitis affect middle aged or elderly individuals and are very rare before age 30 (1, 3, 4, 6, 11, 13). This is the report of a case of sclerosing cholangitis localized at the bifurcation of the common hepatic duct in a 23-year-old patient.

Case Report

A 23-year-old patient was admitted to the hospital complaining of yellowish discoloration of his conjectiva for 40 days. The patient was in good health prior to this development and had never complained before of abdominal pain, anorexia or nausea. His past medical and family history were noncontributory. On physical examination, he was found to be jaundiced, his abdomen was unremarkable, and his stool was clay colored. An x-ray of the abdomen and chest showed normal findings. On admission, pertinent laboratory studies revealed a serum bilirubin 3.9 mg% (direct 2.9; indirect 1.5), alkaline phosphatase 18 units Sivovaro Johns (normal range 2.8-8.6), SGOT 119, SGPT 126. Percutaneous transhepatic cholangiogram demonstrated obstruction at the junction of the two hepatic ducts caused by a one centimeter mass (Fig. 1). The intrahepatic biliary tree was dilated and the distal common hepatic and the common bile duct were normal. Three days later, while the patient was being prepared for exploration, the bilirubin rose to 8.3 mg%.

Upon exploration, the liver, stomach and retroperitoneum were normal. The gallbladder was collapsed, thickened, and filled with white bile. A

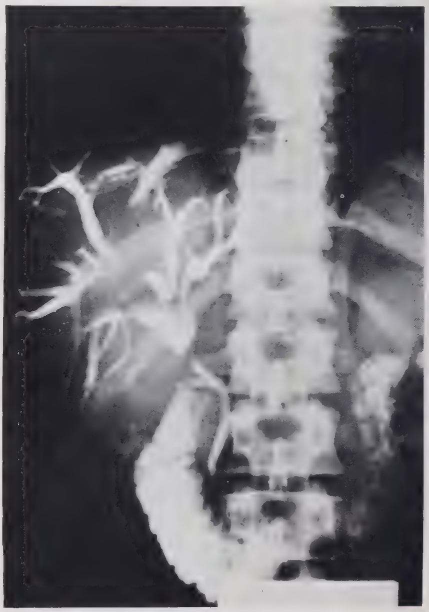

FIG. 1. Percutaneous transhepatic cholangiogram visualizing the dilated intrahepatic biliary tree and the site of obstruction. The common duct is normal.

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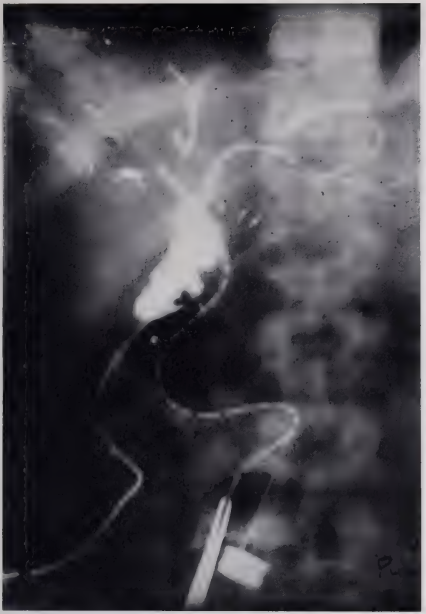

FIG. 2. The resected specimen.

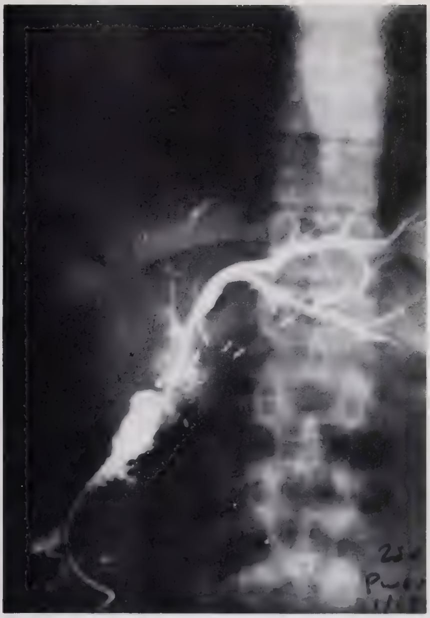

FIG. 3. Postoperative radiologic demonstration of the implantation of the common hepatic ducts into a defunctionalized loop of jejunum. The catheters were left in situ for three months.

two centimeter discrete and extremely hard mass was found at the bifurcation of the common hepatic duct. The common bile duct was normal and the hepatic ducts were dilated. The common duct node was enlarged and removed for frozen section examination which was reported as chronic lymphadenitis. The patient underwent cholecystectomy and en block dissection of the mass including adjacent common duct and common hepatic ducts (Fig. 2). Frozen section examination of transected hepatic ducts showed no evidence in the margins of resection. An end-to-side cholangiojejunostomy using two plastic catheters as stents was then carried out with each hepatic duct. The catheters were pulled through the wall of the jejunal loop and the abdominal wall in order to provide external drainage.

The patient had an uneventfull postoperative course and remains free of symptoms 16 months later. Examination of permanent sections revealed sclerosing cholangitis confined in the bifurcation of the common hepatic duct. The remaining hepatic duct, as well as the common bile duct, were free of disease. The gallblader wall was involved by inflammatory infiltration and adenomyosis, and neoplastic elements were not encountered anywhere.

Discussion

Sclerosing cholangitis localized in a segment of the extrahepatic biliary tree is so rare (3) that its very existence is questioned (11). In general, six requirements have to be fulfilled before a case of obstructive jaundice is classified as caused by sclerosing cholangitis: 1) absence of gallstones and prior biliary surgery 2) absence of carcinoma of the bile ducts 3) absence of biliary cirrhosis 4) absence of retroperitoneal fibrosis 5) generalized thickening and stenosis of the ducts 6) obstructive jaundice (11, 12). According to Longmire (9), obstruction localized in the bifurcation of the common hepatic duct that coexists with dilatation of the intrahepatic biliary radicles should be attributed to cholangiocarcinoma until proven otherwise. Fee et al, however, accept the existence of a rare form of sclerosing cholangitis that affects only a segment of the extrahepatic ducts (3).

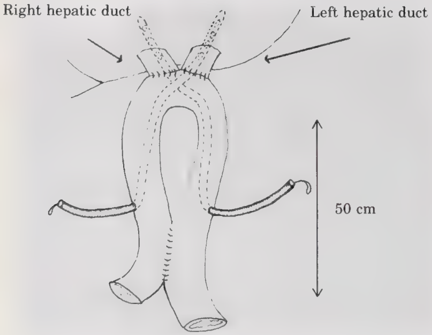

FIG. 4. Representation of the reconstruction operation.

The etiology of sclerosing cholangitis is unknown (3, 11, 12, 14). Immunologic factors (5), polyvinylchloride or tetrafluorocarbon poisoning (3), and portal pyemia in ulcerative colitis (3, 14) have all been implicated. The importance of immunologic factors is strengthened because, experimentally, Schwartzman reaction causes inflammation of the common bile duct (10) in sclerosing cholangitis coexistent with ulcerative colitis and thyroiditis (3). Furthermore, the course of sclerosing cholangitis can be favorably affected by steroid therapy (12). None of these factors was present in this patient, in whom the sclerosing cholangitis was the cause of biliary obstruction. Indeed, in most patients with this disorder the etiology is unknown (12).

The differentiation between sclerosing cholangitis in general and chlolangiocarcinoma of the extrahepatic ducts is very difficult, even histologically (2, 3, 11). Actually, in some patients the diagnosis is confirmed only after a series of reoperations for recurrent jaundice and/or on the autopsy table (11, 7, 2). Frozen section examination is notoriously unreliable (2, 3, 11) so that the surgeon often proceeds on the basis of the macroscopic characters of the disease. Establishment of diagnosis has practical implications because sclerosing cholangitis is managed with intubation of the stenosed duct and with steroids (3, 12, 11, 14), while cholangiocarcinoma requires excision and/or radiation therapy (2, 1, 4, 6, 9, 13).

The lesion in the case presented was treated as a malignancy for three reasons: 1) the patient was young and the disease was confined; 2) the size of the lesion was so small that any attempt to perform biopsy would have traumatized the common hepatic duct; 3) resection rather than intubation is the treatment of choice in the presence of localized sclerosing cholangitis, which if permitted to extend to the remaining extrahepatic biliary tree, has a poor prognosis (7).

Summary

Primary sclerosing cholangitis localized in a segment of the extrahepatic biliary tree is extremely rare. This article describes the case of a 23-year-old male who presented with obstructive jaundice and was found to have primary sclerosing cholangitis of the bifurcation of the common hepatic duct. The lesion was successfully resected.

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The Effect of Prolonged Ethanol Feeding On Exocrine-Endocrine Pancreatic Function

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It is generally accepted that prolonged consumption of alcohol can induce pancreatic exocrine and endocrine dysfunction clinically manifest as chronic pancreatitis in man and experimental animals (1–8). A minimal daily ingestion of 75–80 gm of ethanol over a period of 5–15 years is necessary to produce clinically detectable dysfunction (2).

Sarles et al (6) reported pancreatic lesions similar to those observed in human pancreatitis in rats fed alcohol for 20–30 months. The pathologic findings in these alcoholic rodents included: 1) reduction in acini, 2) ductular reduplications with 3) intraductual proteinaceous plugs, 4) intraductal calculi and 5) occasional beta cell islet adenomas. From a similar study, Huttunen et al (8) reported that chronic ingestion of alcohol resulted in decreased protein concentration as well as increased proteolytic enzyme activity in the pancreatic juice of the rodents.

This study was performed to investigate the sequential alterations of both exocrine and endocrine function induced by prolonged alcoholic ingestion.

Materials and Methods

Sixty male rats (170–180g) of Wistar strain were used. The rats were maintained on a diet of Oriental Chow (MF) ad libitum containing 25% of protein and 6% of the total caloric value as fat together with starch. The rats were randomly divided into two groups. Group 1 (20 rats) was given water freely and group 2 (40 rats) was given 20% ethanol during the experimental period. After the administration of 20% ethanol for 24 weeks, group 2 was subdivided into two groups. One subgroup was allowed to continue the control diet and the second group was given a low protein diet containing 6% and 2.7% of total calories as protein and fat, respectively.

Experiment 1: Eight rats on alcohol and eight control rats were killed after 24 weeks. The rats were weighed and autopsied. The entire pancreas was weighed and fragmented. All specimens were incubated 45 minutes in 2 ml of KRBB (ph 7.4). Incubation was carried out at 37°C with continuous shaking at 60–80 cycle/min. The incubation media were assayed for total protein, amylase and Zn concentrations. The parameters studied were expressed as OD/mg wet weight, U/mg wet weight and 10^{-2}/mg wet weight, respectively.

Experiment 2: Oral glucose tolerance testing (GTT) was performed after 12-hr fasting. Twenty percent glucose solution (2g/kg) was administered orally by metal catheter attached to a 5 ml syringe. Blood (0.05 ml) was collected from the tail vein prior to, and 30, 60, 120 minutes after the glucose administration. A GTT was performed at the first, fourth, eighth, 24th, and 80th weeks of the experiment.

Amylase activity was determined by the method of Caraway. Total protein concentration was measured by absorbance at 280 nm, and Zn concentration was determined by atomic absorption. Glucose was measured by the glucose oxidase method and the insulin was determined by using double antibody radioimmunoassay.

Results

Change of body weight. At the start of this study, the mean body weight of control group and ethanol group was 162 ± 9 (μ ± SD), 174 ± 12g, respectively. When the ethanol group was sub-

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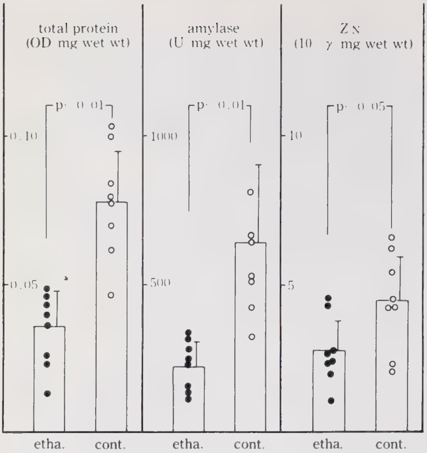

FIG. 1. Protein, amylase, and Zn media concentrations from pieces of rat's pancreas after 24 weeks of 20% ethanol feeding. Each parameter shows a significant decrease in the alcohol feeding rats.

divided the mean body weights of control group, the ethanol group with low protein diet and the ethanol group with control diet was 440 ± 51g, 398 ± 63g and 354 ± 44g, respectively. At the end of the study, the mean body weight was 615 ± 55g, 460 ± 55g, and 375 ± 75g, respectively. There was a significant difference (p 0.02) between the control group and ethanol groups.

Basal exocrine pancreatic function. Figure 1 presents the concentration of protein, amylase, and Zinc in the minced whole pancreas of control and alcoholic rats at 24 weeks. The alcoholic animals showed significant reductions in the concentrations of protein and amylase. The Zinc concentration in the alcoholic rats was lower than in the controls, the difference was not statistically significant.

Glucose tolerance studies. The sequential changes in mean glucose tolerance in control and alcoholic rats are plotted in Figures 2 and 3. None of the alcoholic rodents became diabetic. Instead, there is a clear trend throughout for the blood glucose responses to be lower in alcoholic animals than in the control rats. During the later periods of study, that is, 15–20 months, the flattenings of the curve becomes more pronounced and the fasting blood sugars of the alcoholic rats becomes statistically significant lower than observed in the controls.

Changes in insulin response. Figure 4 compares the insulinogenic index (increase in plasma insulin/increase in plasma glucose) during GTT. At 30 minutes in the fourth week, the index was 1.8 ± 0.8 for the control compared to 0.7 ± 0.44 for the alcoholic animals. By the eighth and 24th week, this difference in indices is no longer present nor statistically significant.

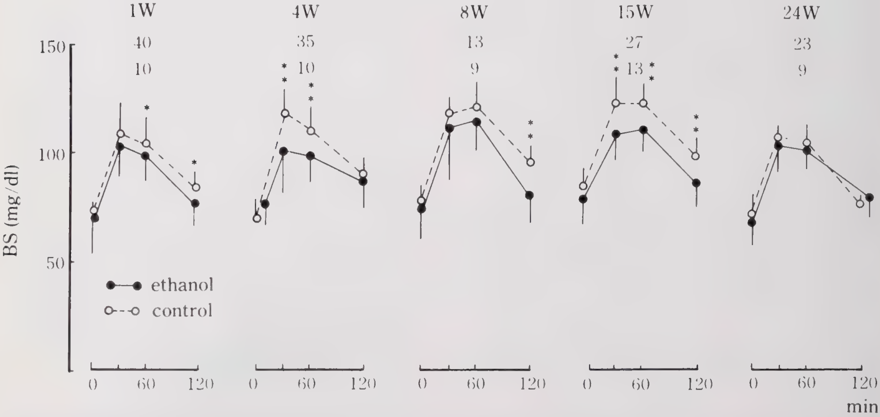

FIG. 2. Sequential glucose tolerance curves up to 24 weeks after ethanol feeding. In ethanol fed rats', a significantly lower blood glucose level during GTT was observed, that is, at 60 and 120 minutes after one week of ethanol feeding, at 30 and 60 minutes after four weeks, at 120 minutes after eight weeks, and 30, 60, and 120 minutes after 15 weeks.

(*p 0.05, **p 0.01)

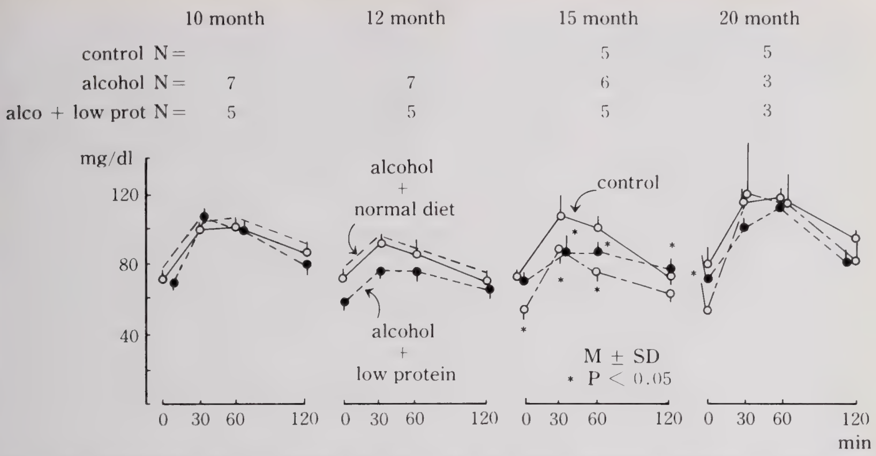

FIG. 3. Sequential glucose tolerance curve from 10 months to 20 months after ethanol feeding. The fasting glucose level was lower in the ethanol groups compared to the control group.

In Figure 5, glucose tolerance curves and plasma immunoreactive insulin levels are plotted at the 20th week for control animal, alcoholic animals with a normal diet, and alcoholic rats fed low fat diets. It is clear that the alcoholic animals have a statistically significant lower fasting blood sugar as well as lower plasma insulin level. Insulin release following glucose does not appear to be impaired but plasma insulin concentration return to statistically significant lower levels in the alcohol fed rats.

Discussion

While there is general agreement that prolonged ingestion of ethanol results in pancreatic inflammation in man and experimental animals (1,2), there is considerable differences of opinion as to the pathogenesis of this inflammation and also the effects of long term alcoholism on the exocrine-endocrine function. Thus, Sardesai et al (9) have shown that intragastric alcohol feeding in rodents for 40 weeks decreased protein synthesis in the pancreas by almost 50%. Sarles et al (6), on the other hand, reported protein precipitates in the pancreatic juice of rats after 20% ethanol feeding for 20–30 months. After three months of intragastric ethanol feeding in the dog, Tiscornia et al (7) reported significant depression of pancreatic flow and bicarbonate secretion, protein output remained unchanged, while protein concentration in pancreatic juice was significantly increased. These changes were explained by the following hypothesis: the administration of alcohol induced a suppression of secretin and an augmentation of gastrin release from the duodenum as well as an increase in cholinergic (vagal) tone. The findings in this study, that is, increased concentrations of protein and enzyme in the exocrine pancreas after prolonged alcohol feeding, are in agreement with those of Sarles (7) and indicate an alcohol induced alteration of pancreatic acinar function at the cellular level.

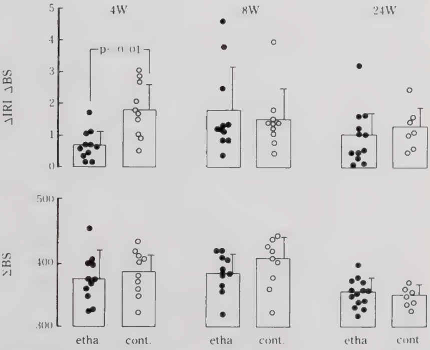

FIG. 4. Insulinogenic index at the 30 minutes during GTT. After four weeks of ethanol feeding, there was a significant difference between the ethanol group and the control group.

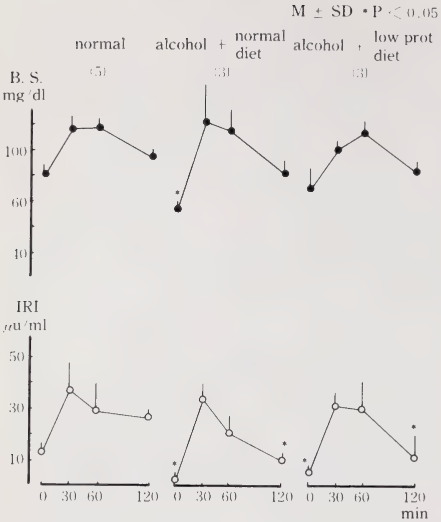

FIG. 5. Glucose tolerance curve and insulin response curve during GTT after 20 months of ethanol feeding.

A number of investigations have dealt with the effect of chronic alcoholism on glucose tolerance and pancreatic endocrine function in experimental animals. Gerard et al (13) found increased mean serum glucose levels in moderate drinkers (six to eight alcoholic drinks/day). However in heavy drinkers (nine or more drinks/day), the mean plasma glucose levels were lower. The effect of ethanol ingestion on insulin secretion is also controversial. Kuhl et al (14) reported that a serum ethanol concentration of 10 mM induced a more than threefold increase in insulin secretion as compared to saline, while serum ethanol concentrations of 19 mM did not affect the serum insulin levels in the pig. Kuo et al (15) reported that alcohol stimulated insulin release, Jauhonen (16) noted no effect, and both Shah et al (12) and Colwell et al (17) found that alcohol suppressed glucose-induced and tolbulamide-induced insulin release in rodents and canines. The present data, fasting plasma glucose concentration, glucose tolerance tests, plasma insulin levels, and insulinogenic index clearly indicate that prolonged alcohol ingestion does effect pancreatic endocrine function. The discordant findings of Kuhl et al (14) and Jauhonen et al (16) probably arose because of differences in duration, dosage, and route of administration of ethanol.

Protein-calorie malnutrition has been reported to affect pancreatic function (18,19), that is, a high incidence of diabetes has been reported in protein deficiency calcific pancreatitis (20). The results in this study failed to indicate a difference in endocrine function in the alcoholic rats fed a normal diet and those kept on a protein deficient diet.

Conclusions

Prolonged alcohol feeding results in disturbances in endocrine as well as exocrine function in the rat. These disturbances are not significantly altered by low protein feeding.

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Intracellular Amyloid in Trabecular (Merkel Cell) Carcinoma of Skin: Ultrastructural Study

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Eugene Marquet, M.S.,† and Harold J. Sobel, M.D.††

Abstract

Dermal tumors arising from cells equated with the Merkel cell are quite common. They appear as growths composed of poorly differentiated cells. Cytoplasmic dense core granules may be found ultrastructurally. Amyloid between or within the tumor cells is commonly observed.

Introduction

The malignant skin tumor variously described as trabecular carcinoma, Merkel cell carcinoma, neuroendocrine or neuroepithelial carcinoma comprises a distinct clinical, histologic and ultrastructural entity. The various names applied to it allude to its light and electron microscopic features and presumed histogenesis. It is the purpose of this paper to report three further cases studied ultrastructurally and to show that amyloid production is a feature of this neoplasm.

Materials and Methods

The surgical specimens were routinely fixed in formalin, embedded in paraffin and stained with hematoxylin and eosin. Amyloid was stained with Congo Red and viewed in polarized light. The Fontana-Masson and Grimelius procedures were utilized in an attempt to demonstrate cytoplasmic granules.

Paraffin embedded material from the first two cases and formalin fixed wet tissue from the third case were examined with an electron microscope (1–4).

Case Reports

Case 1: A skin tumor measuring 2.5 cms was removed from the right deltoid area of a woman 83 years of age. This mass had been present for several months. Microscopic study showed an incompletely removed trabecular carcinoma of the skin. A wider excision disclosed microscopic residual tumor. The patient has had no recurrence of the lesion.

Case 2: A slightly red subcutaneous mass "the size of a quarter" was observed on the superolateral aspect of the right knee of a 71-year-old woman in April 1979. Clinically, the differential diagnosis was lipoma, sebaceous cyst or hemangioma and the lesion was excised in August 1979. The biopsy was reported as trabecular carcinoma and the patient underwent a wide local excision of the operative site in October 1979. No residual tumor was found in the specimen. The patient was followed at regular intervals and has remained free of tumor for a while. She entered Memorial Hospital for recurrent disease and died of widespread dissemination of her tumor in May 1981.

Case 3: A 75-year-old man presented with a 10-year history of having neoplasms removed. Most of these tumors were basal cell carcinomas; one was a squamous cell cancer and another one was a pilomatricoma. He had been treated with topical 5-fluorouracil to control keratoses and their sequelae.

During the antecedent three or four months,

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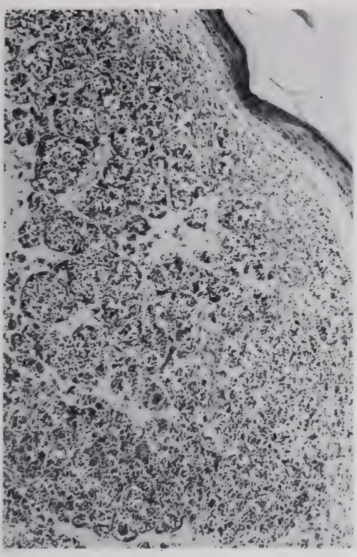

FIG. 1. Low magnification of loosely arranged tumor cells in dermis. Scattered multinuclear giant cells are noticeable (Case 3) (H. & E. 76×).

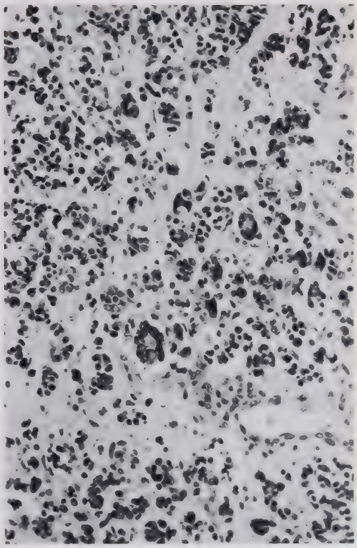

FIG. 2. Higher magnification of similar area. Most cells are small and round or oval with scant cytoplasm. The giant cells are readily seen (Case 3) (H. & E. 195×).

the patient noticed an "enlarging pimple" present on his back. This lesion was excised in January 1980.

A recurrence was removed in May 1980 and also studied with the electron microscope. No further cytoplasmic dense-core granules were noted. Intracytoplasmic amyloid, however, was still present.

Results

The routine microscopic findings were identical to cases published or previously seen and will not be elaborated upon. Case 3 showed scattered multinuclear giant cells only in its more superficial parts (Figs. 1–4). The Congo Red stain was invariably positive. The Fontana-Masson and Grimelius silver impregnation failed to bring out cytoplasmic granules.

When viewed with the electron microscope, the tumors were composed of small cells with a high nuclear-cytoplasmic ratio. The nuclei were round or oval with few irregularities of outline. Chromatin clumping was prominent. Nucleoli were large and often double.

There were moderate numbers of small desmosomes and occasionally better developed desmosomes with condensed clusters of 70 nm filaments between cells were noted (Fig. 6). Numerous cytoplasmic ribosomes and polyribosomes were noted as well as a prominent Golgi apparatus (Fig. 5) and large collections of paranuclear filaments (Fig. 7). Membrane bound, dense-core granules were found only in case 3 (Figs. 5, 6).

Peculiar paranuclear tubular structures seemingly related to the endoplasmic reticulum were seen frequently in all cases (Fig. 6). These structures were composed of closely placed tubules often cut in cross section. The bundles of cytoplasmic filaments were seen in most cells of all three cases. They were irregularly interwoven, about 100 nm thick and beaded. Their appearance was characteristic of amyloid.

Discussion

Historically, in 1972 Toker (5) described as trabecular carcinoma of the skin, a dermal or subcutaneous cancer composed of rather uniform small cells. He proposed derivation from immature cells present within the dermis or subcutis capable of differentiation into primitive sweat glands. In 1978 and 1979, Tang and Toker (6, 7) next reported an additional 12 cases of this entity.

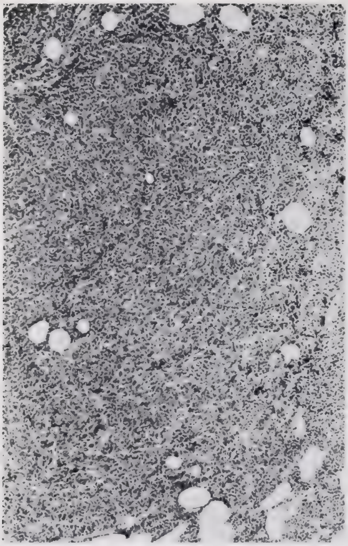

FIG. 3. A dense area of the tumor discloses residual adipose tissue of the subcutis (Case 3) (H. & E. 76×).

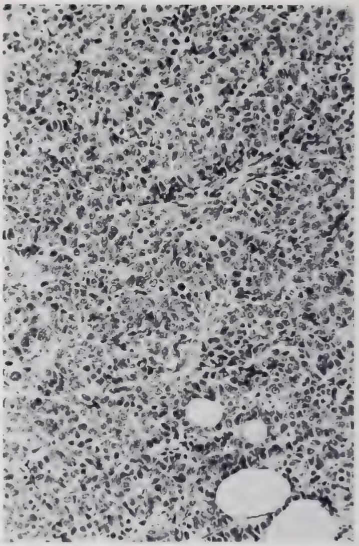

FIG. 4. Higher magnification shows numerous mitotic figures (Case 3) (H. & E. 195×).

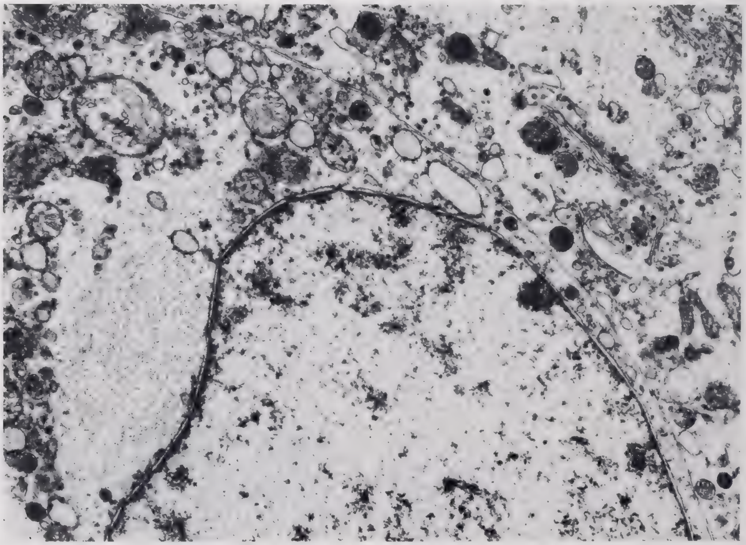

FIG. 5. Electronmicrograph shows paranuclear collection of filaments, prominent Golgi apparatus, distinct dense core granules and several small desmosomes (Case 3) (16000×).

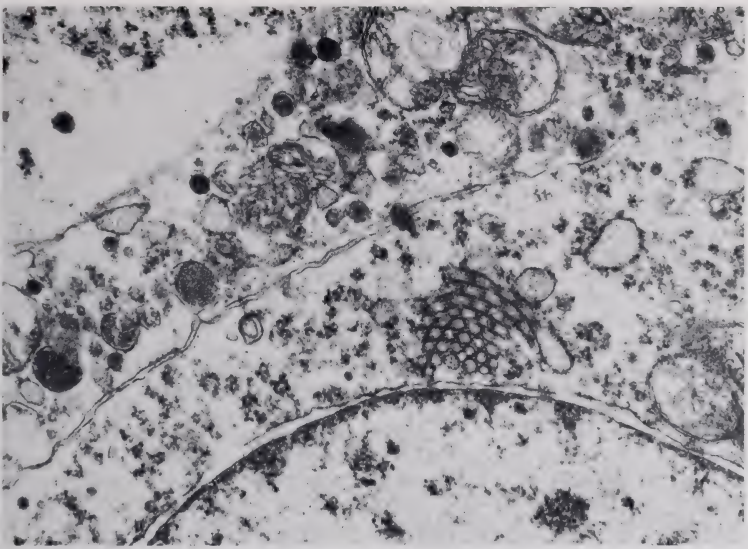

FIG. 6. Dense core granules, ribosomes and polyribosomes and a well developed desmosome (above center). The latter shows small tonofilaments. The aggregate of tubular profiles appears related to the endoplasmic reticulum (Case 3) (32000×).

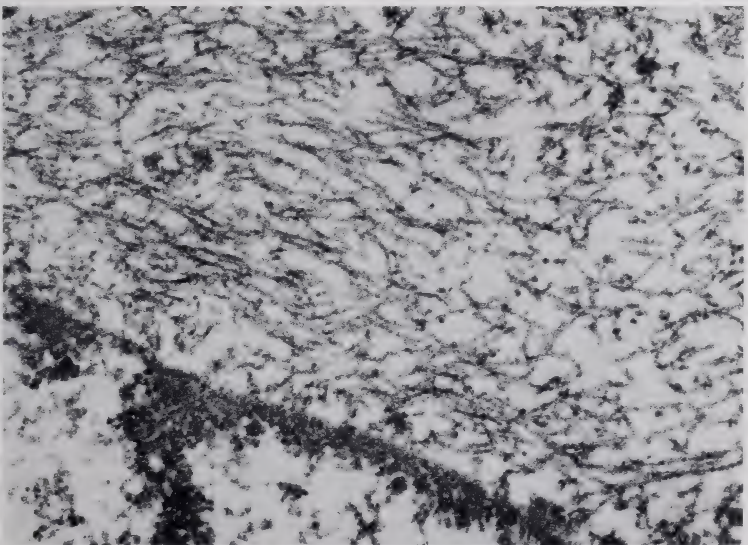

FIG. 7. Prominent collection of 100 Å filaments in paranuclear area (Case 2) (66000×).

Electron microscopic examination of six cases revealed the presence of neurosecretory granules in the cytoplasm of the tumor cells. The ultrastructural features of the tumor cells suggested to them a neural crest origin from the Merkel cells present in the epidermis and dermis.

At the same time, Abaci and Zak (8) demonstrated histochemically and ultrastructurally the presence of extracellular and intracellular amyloid in a patient with multicentric lesions.

Sidhu et al (9) described seven of these malignant skin tumors as Merkel cell neoplasms based on the ultrastructural similarity of the neoplastic elements with normal Merkel cells. Sibley et al (10) published another seven cases as neuroendocrine carcinoma of the skin and Silva and Mackay (11) reported 11 cases as small cell neuroepithelial tumors of the skin based on their electron microscopic features.

Most workers favor the derivation of this neoplasm from Merkel cells. These specialized cells have been identified in the epidermis, dermis, oral mucosa, common and vibrissal hairs, and nails of man and all mammals, as well as in the epidermis of birds, reptiles, (12) amphibians (13), and teleost fishes (14). They are believed to be slow adapting, modality-specific mechanoreceptors involved in the mediation of touch and the movement of hair. They generally appear as innervated clusters (variously named Haarscheibe, touch pads, touch corpuscles, hederiform endings of Merkel-Ranvier, organ of Eimer, tactile hair disc of Pincus, Iggo dome), but may also occur singly.

With light microscopy the Merkel cell appears as a medium sized "clear" cell present within the basal region of the epidermis. Munger (15) considered reports of dermal Merkel cells as sectioning artifacts, although they have been observed in this location in the human fetus (16, 17), and in the hair root sheath of adult man (18). On electron microscopy the Merkel cells are seen attached to adjacent keratinocytes by well-defined desmosomal junctions and spinous cytoplasmic processes (19). They are also in close relationship with expanded axon terminals. The nucleus is generally lobulated and has been found to contain a characteristic filamentous "rodlet" inclusion in human oral mucosa (Fortman and Winkelman (20) and rabbit epidermis (21). The cytoplasm of the Merkel cell contains numerous dense-cored membrane bound granules, bundles of microfilaments, abundant free ribosomes, mitochondria, glycogen, lysosomes, and vacuoles. The Golgi complex is well formed and the rough endoplasmic reticulum is usually poorly developed. The secretory granules are 80–100 nm in diameter, often aggregate near the Golgi region and are generally polarized toward the neurite (15).

The trabecular carcinoma occupies the dermis, often extending into the subcutaneous fat, occasionally invading dermal lymphatics, but generally does not involve the epidermis and its adnexa. A lymphocytic infiltrate is often present at the periphery of the tumor. On light microscopy these neoplasms are composed of sheets, clusters, and anastomosing cords of small round cells with scant cytoplasm and prominent dark nuclei. Occasionally, there are rosette-like formations (6, 7). The nuclei are round or oval, with dispersed chromatin and generally inconspicuous nucleoli. Mitoses are often numerous. In some instances portions of the neoplasm have been reported as showing squamous differentiation (7, 9).

Ultrastructurally, the neoplastic cells are polygonal, with occasional surface microvilli and puncta adherentia junctions (10). They have nuclei which are round or lobulated, with finely dispersed chromatin and small nucleoli adjacent to the nuclear membrane. The cytoplasm contains scant rough and smooth endoplasmic reticulum, a prominent Golgi complex, numerous polyribosomes, few mitochondria, perinuclear microfilaments, glycogen, and dense-cored granules. The numerous ribosomes are responsible for the pyroninophilia of the neoplastic cells (9). In some instances, granulogenesis from the Golgi complex has been noted (9). Sidhu et al (9) observed intranuclear filamentous inclusions in one of their cases which were identical with the "rodlet" found in normal Merkel cells (20, 21). Basal lamina material, tonofilaments and melanosomes are absent.

Abaci and Zak (8) first demonstrated ultrastructurally and histochemically the presence of extracellular and intracellular amyloid in this type of lesion. Perinuclear bundles of microfilaments were observed in two of the six cases of Tang and Toker (6, 7) and in three of the six cases of Sibley et al (10) studied ultrastructurally. Sibley et al (10) considered the possibility of amyloid, however, congo red staining was negative. The significance of amyloid in this tumor is unclear with regard to its histogenesis. Amyloid occurs in a variety of benign and malignant skin growths, especially basal cell carcinoma (22). It has also been found in association with a variety of endocrine tumors (23, 24). It is possible to distinguish the so-called APUDamyloid of these endocrine neoplasms from the immunamyloid of systemic disorders by immunofluorescence (23). The intracytoplasmic location of the amyloid fibrils found with trabecular carcinoma also occurs in other human tumors; however, it is uncertain whether it is actively produced intracellularly or is a result of phagocytosis (8). The subject of the pathogenesis of amyloid deposits and amyloidosis has been extensively reviewed recently by Glenner (25). The ultrastructural features of trabecular carcinoma led Tang and Toker to propose an origin for this neoplasm from Merkel cells, a presumed member of the APUD series within the skin. Ultrastructurally, the demonstration of synaptic contacts within the Merkel cell-axon complexes is suggestive of neuroreceptor function (26). The cytoplasmic membrane-bound dense-cored granules are characteristic of neuroendocrine cells and are believed to store biogenic monoamines or polypeptide hormones involved with neurohumoral or hormonal activity. These features along with the presence of an intranuclear rodlet also found in neurons, the occurrence of esterases, and the argyrophilia of the Merkel cells of certain species caused Winkelmann (27) to conclude that they were APUD system members.

However, the full body of evidence is not in agreement with this. Histochemically, the Merkel cell shows marked pyroninophilia, has a light PAS reaction, and generally lacks argyrophilia or argentaffinity.

The histochemical nature and function of the intracytoplasmic dense-cored granules within the Merkel cell is unclear. While they have been observed to fuse with the cell membrane at Merkel-cell-neurite (synaptic) regions (28), the failure to demonstrate catecholamines by fluorescence microscopy (29), or other histochemical methods (30), and the inability to induce excitation with various pharmacologic agents (29) challenges their participation within the traditional concept of neurohumoral transmission. However, a stored substance may still be released into the local environment to act in a paracrine fashion. In this regard, immunohistochemical studies of Merkel cells in the epidermis of the rat have shown met-enkephalin-like reactivity, indicating the presence of a polypeptide substance (26).

Pearse (31) while listing the Merkel cell along with the melanocyte as neuroendocrine cells of the skin, conceded that it did not possess the full complement of biochemical characteristics of other APUD members. Additionally, he stated that a neural crest origin for the Merkel cell was still hypothetical and that evidence for the transformation of the normal Merkel cell into these undifferentiated skin neoplasms was incomplete. Moreover, Tweedle (13) demonstrated the presence of Merkel cells in the digits of amphibian larvae in which all the neural tissue, including the neural crest, was removed.

There have been reports of cutaneous tumors believed to be hormonally active which suggest that APUD elements may be present in the skin. Johannessen and Gould (32) reported a skin carcinoma associated with calcitonin production which they suggested might be a Merkel cell carcinoma. In a later study, Gould et al (33) reported on two additional primary skin carcinomas also studied by electron microscopy and immunohistochemistry. The latter disclosed calcitonin and somatostatin in the cells of all cases and ACTH in one case. Van Dijk and Seldam (34) described as a possible primary cutaneous carcinoid an organoid tumor which was argentaffin positive and associated with flushing. However, it should be noted that there is no evidence that any of the listed cases of trabecular carcinoma has been found associated with any systemic syndrome.

The basal cell carcinomas containing amyloid, argyrophilic cells and secretory granules studied by Eusebi et al (35) suggested to them an aberrant endocrine differentiation from the epithelial germ cells of Pinkus. They considered but dismissed the Merkel cell as the source of these endocrine elements because cytoplasmic filaments had not been found in it. Revuz et al (36) also demonstrated secretory granules in the intraepidermal pagetoid cells of Woringer-Kolopp disease and considered it a Merkel cell disorder.

Theories of the histogenesis of the Merkel cell include an origin from neuroectodermal or epidermal elements. It has been claimed that the Merkel cells are of neural crest origin, migrating through the dermis and entering the epidermis by invading the basal lamina. This is supported by the common finding of Merkel cells in the mesenchyme and epidermis of mammalian embryos (17), whereas they are rarely observed in the dermis of adult forms (18, 37). Hashimoto (16) demonstrated in human skin that Merkel cells were abundant in the dermis in fetal life, with migration into the epidermis almost complete at birth.

The theory of the epidermal origin of the Merkel cells claims derivation from epithelial keratinocytes. This is supported by the discovery of transitional elements which have features of both of these cells (12, 38). English (12) has shown the presence of cells with tonofibrils and secretory granules in the epidermis of the rat, whereas Nafstad (38) reported granulated basal cells in the snout of the pig.

The occurrence of the vast majority of these tumors in the dermis is puzzling. Sidhu et al (9) proposed as a possible explanation for their der-

TABLE I

Author And Year	Age & Sex	Location	Duration Before Surgery	Size of Tumor (cm)	Local Recurrence	Status at Last Follow-up	Lymph Node and Soft Tissue Metastases	Duration of Metastases	Duration Follow-up
Toker—1972									
1	65 F	forearm	3 mos	1.0	none	alive & well	—	—	8 yrs
2	70 F	leg	—	1.5	twice	alive & well	—	—	10 yrs
3	65 F	face	1 yr	1.5	none	alive & well	+	4 yrs	10 yrs
4	76 M	lip	4 mos	2.5	none	died of unrelated causes	+	3 yrs + 6 mos	3 yrs + 6 mos
5	75 M	buttock	2 yrs	3.0	massive	died of disease	+ +	—	2 yrs + 3 mos
Tang & Toker 1978									
6	72 F	leg	—	1.5	none	died of unrelated causes	+	—	5 mos
7	76 M	thigh	—	0.6	none	—	—	—	—
8	92 F	cheek	long	3.5	none		—	—	6 mos
Abaci & Zak 1979									
9	75 M	5 head 1 chest wall 1 knee	7 mos	none over 1.5	none	died of unrelated causes	-	—	metastases to liver
Tang & Toker 1979									
10	48 M	arm	over 2 mos	5.0	none	alive & well	forearm		2 yrs
11	74 F	cheek	months	7.5	at surgical site	alive & well	—		7 mos
12	68 F	arm	unknown	fungating	?	not returned for follow-up	+		6 mos
13	63 M	gluteal region	several months	3.0	none	died of unrelated causes	—		4 yrs
14	67 F	cheek	unknown	1.0	none	alive & well	—		1 yr
15	Mid. Age M	knee	6 mos	0.7	none	alive & well	+		7 yrs + 1 mo
16	61 M	digit	unknown	1.5	3 months after 1st incision	alive & well	+		5 yrs + 7 mos
17	46 F	pre-tibial area	unknown	2.0	none	alive & well	+		10 yrs
18	71 F	foot	unknown	less than 2 cm	?	lost to follow-up	+		—
Sidhu—1980									
19	61 M	eyelid	8 mos	3.0	twice	alive & well	+	9 mos	1 yr + 1 mo
20	76 F	cheek	—	1.0	four times	alive & well	+	5 yrs	5 yrs + 7 mos
21	70 F	elbow	1 mo	—	none	alive & well	—	—	7 mos
22	51 M	thigh	8 mos	—	none	alive & well	+	2 yrs + 6 mos	3 yrs + 6 mos
23	70 F	thigh	18 mos	4.0	none	alive & well	—	—	5 mos
24	57 M	cheek	—	—	once	alive & well	+	11 mos	3 yrs
25	57 M	eyelid	2 mos	0.6	none		—	—	—
Sibley, et al 1980									
26	82 M	cheek	—		extensive	—	+	—	—
27	77 F	ear	—		extensive	—	+	—	—
28	84 M	knee	—	3.0	none	alive & well	+	—	1 yr
29	69 F	buttock		5.0	none	alive & well	—	—	1 yr
30	63 M	leg		1.0	none	alive & well	—	—	14 yrs
31	49 F	elbow		1.5	none	not returned for follow-up	—	—	—
32	89 F	thigh		0.8	none	not returned for follow-up	—	—	—
Silva, et al 1980									
33-43	56-84 (median 69 yrs)	7 head & neck 4 rest of body	—		3 cases	3 cases died at 6, 18 & 20 months after excision of primary lesion	6 cases	—	—
Gould et al 1980									
44	60 F	temple	unknown	2 cm	four	alive	systemic	—	10 yrs +
45	69 F	oral commissure	unknown	2.5	once	died after 38 mos	lung & liver	20 mos	3 yrs + 2 mos
46	65 F	cheek	unknown	1.5	none	alive & well	+	—	3+ years

Note: Stern (1980) (personal communication) has 30 cases in the material of the AFIP. Some of these do not contain dense-core granules.

mal location, the theory that the Merkel cells present in the epidermis were totally differentiated whereas undifferentiated precursors capable of neoplastic proliferation remained in the dermis. While uncommonly found in human dermis (37), it is possible that residual mesenchymal Merkel cells still exist there. On the other hand, the reverse migration of Merkel cells from the epidermis to the dermis remains a possibility. Tumors have been reported that also involve the epidermis and which contained both squamous and Merkel cells (9), or trabecular components (6). Electron microscopy in case six of Sidhu et al (9) showed a transition in differentiation from the Merkel cell to the squamous elements, causing them to suggest the existence of a common precursor cell. Tumors composed of neoplastic basal cells containing neurosecretory granules have been observed in man (35).

The reported cases of trabecular or Merkel cell carcinoma are summarized in Table I. There appears to be no sexual predilection, with 17 females and 15 males recorded. The tumor favors old patients, with a reported age range of 46–92 years, and a peak incidence in the seventh and eighth decades. Among 38 lesions in which the anatomic site was specified, 16 occurred on the face, 18 on the extremities and four on the back. The majority of the lesions are small, being under 2 cms in diameter. The tumors measuring 5 cms and 7.5 cms reported by Tang and Toker (7) are the largest recorded. The tumor generally presents as an asymptomatic nodular swelling in the skin, but occasionally there is an inflammatory component. Virtually all the lesions are situated in the dermis, with extension into the epidermis only reported in one case each by Tang and Toker (6) and Sidhu et al (9) and in two cases by Silva and Mackay (11).

Wide local excision appears to be the treatment of choice for trabecular carcinoma. Local recurrence was reported in 12 cases following simple excision. Radical lymph node dissection is reserved for the appearance of regional metastasis. The incidence of regional metastasis is about 50% (22 of 43 cases). There appears to be no correlation between the size of the primary tumor and the development of lymph node spread. While regional metastasis generally appear within one year, occasionally they are deferred for four or five years (5, 9). Although long term follow-up is lacking in many of the reported cases, prolonged survival despite regional metastasis is not unusual following radical lymph node dissection. In five instances, death could be directly attributed to the tumor. The patient of Abaci and Zak (8) had liver metastasis but died of other causes, and that of Sibley et al (10) was alive with spread to the fibula.

Radiotherapy offers limited control of these lesions. Temporary regression was reported in two of the five cases of Tang and Toker (7) following irradiation and temporary regression was reported in one case of Sibley et al (10). In the few instances that chemotherapy had been employed, it also provided only limited benefit.

Pathologically, neoplasms of Merkel cells have been misdiagnosed as primary cutaneous carcinomas (for example, poorly differentiated sweat gland and squamous cell carcinoma), cutaneous metastasis of visceral neuroendocrine carcinomas (for example, oat cell carcinoma, islet cell tumor, carcinoid tumor, neuroblastoma), and large cell lymphoma. Electron microscopy is generally necessary to establish the correct diagnosis beyond doubt.

Addendum

We recently reviewed a biopsy of a recurrent skin tumor of the elbow removed from a woman 66 years old. There was striking mitotic activity. Electronmicroscopy revealed dense core cytoplasmic granules as well as small intercellular junctions. Amyloid was absent.

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Vision Loss in Cranial Arteritis: Relation to Corticosteroid Therapy

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Abstract

Fifty-one patients with biopsy proved cranial arteritis were retrospectively studied to assess the relationship between steroid administration and vision loss. It was found that the major risk to vision loss occurred early in the disease. In only one case did vision loss occur after 96 hours of high dose (>60 mg of prednisone equivalent) steroid treatment, even with flare-up of disease concomitant with steroid withdrawal.

It is concluded that high dose steroid treatment need be used only early in the course of the disease.

Cranial arteritis is a granulomatous angiitis affecting the elderly (1). One of its major complications is vision loss due to involvement of branches of the ophthalmic artery with resultant ischemic optic neuropathy (2). With the introduction of corticosteroids in the treatment of cranial arteritis, the incidence of blindness as a complication has markedly decreased (3). Though there have been no controlled prospective studies on the use of corticosteroids, it is universally agreed that steroids probably prevent vision loss in the majority of patients and all clinicians use steroids as standard treatment (4).

A more difficult and yet unresolved question is the duration and dose of steroid administration. It is clear from many studies that cranial arteritis may remain active for many years (5), but the long-term use of corticosteroids is obviously associated with the high risk of serious ill effects, particularly in the elderly. This high risk could be justified if patients continued to be subject to the risk of blindness but would not be justified if the risk of vision loss was minimal. In reference to this question, we have reviewed our experience with 51 patients seen in private practice, with biopsy proven cranial arteritis.

Materials and Methods

There were 51 patients in the group ranging in age from 48 to 90. All patients had a temporal artery biopsy diagnostic of cranial arteritis. There were 38 women and 13 men. Of the entire group, 11 had loss of vision; eight became totally blind, two patients lost all vision in one eye and partial vision in the other eye, and one patient lost all vision in one eye. In all patients with vision loss, the ophthalmologic appearance was that of ischemic optic neuropathy. None had a central retinal artery occlusion.

Of the eight patients who became totally blind, six were blind before the patients were seen by us and the correct diagnosis considered. One of the blind patients had lost all vision in one eye and partial vision in the other eye when first seen and, in spite of high doses of steroids, became completely blind within four days. The other had suffered headache and fever for three months and was seen by one of us when already blind in one eye for two weeks. Despite being started on 120 mgm of prednisone daily she became totally blind in another week. It is very possible that early diagnosis and treatment could have saved her sight. One patient had lost vision in one eye before referral and treatment, and then had no subsequent decrease in vision. Another patient who had normal vision before the institution of corticosteroids became totally blind in one eye and lost three quarters vision in the remaining eye while on high doses of corticosteroids, while another lost

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TABLE I
(Total Patients 51)

	Vision Loss (")	No Vision Loss
Headache	10/11 (91%)	28/40 (70%)
CNS Symptoms	3/11 (27%)	5/40 (12.5%)
Elevated ESR	9/11 (82%)	40/40 (100%)
Associated Polymyalgia Rheumatica	2/11 (18%)	15/40 (37.5%)
Died	2/11 (18%)	6/40 (15%)
Males	5/11 (45%)	8/40 (20%)

all vision in one eye and three quarters vision in the other eye before steroids were instituted. Thereafter, her vision remained stable.

The following Table I presents some pertinent features in this series. It compares the groups who did and did not lose vision and notes the surprisingly high percentage of males in whom sight was lost.

Despite the usual preponderance of females, it is interesting to note that 45% of those losing vision were males. At present, we have no explanation for this seeming variation. Of further interest in our series of cranial arteritis, we found 17 of 51 (33%) to have associated Polymyalgia Rheumatica (P.R.). In our series of some 500 cases presenting as P.R., only three have developed cranial arteritis, none of whom lost vision.

As seen in Table I, eight of 51 patients died, and in only one instance (dissecting aortic aneurysm) was the arteritis the direct cause of death. It would follow then, that careful steroid therapy not only largely prevents blindness but is highly effective in limiting the disease generally.

The patients have been followed for one to ten years. In only one case (see above) did sight diminish further after the first four days of treatment with high doses of steroids, even with subsequent flare-ups of cranial arteritis associated with tapering of steroids. Many of these patients again developed headaches or, more commonly, myalgic fevers, but no vision loss ensued. There have been nine deaths; one died of chronic lymphatic leukemia and one of gastric carcinoma. The other seven died of vascular disease; one of a cerebral vascular accident, one with a dissecting aneurysm of the aorta and five of coronary artery occlusion. Postmortem examination of the patient who died of an aortic aneurysm showed active giant cell arteritis in the area of dissection. But this patient's arteritis was only discovered at autopsy. She had never been treated with steroids, never had ocular symptoms and had not been under our care. A 72-year-old woman who died of an acute coronary occlusion had been in clinical and laboratory remission of her arteritis and not taking corticosteroids for two years. The coronary occlusion proved to be on the basis of atherosclerotic disease. However, she had evidence of active arteritis involving many of her vessels including the aorta, superior and inferior mesenteric and iliac arteries. Of the other five who died of arteriovascular disease, three had low grade active arteritis at the time of their death and two were in clinical remission and not on corticosteroids. We have no knowledge that active arteritis played a role in their demise, but at no time were eye symptoms clinically evident after initial therapy for cranial arteritis.

Discussion

The above data again emphasize that vision loss is a significant and, unfortunately, a frequent complication of cranial arteritis. In this series, 11 of 51, or 21%, had some loss of vision. However, if those patients in whom vision loss occurred before institution of treatment were excluded, only two patients lost vision after treatment was begun. In addition, in only two other patients was there progression of vision loss over the first few days of steroid treatment. It therefore seems highly significant that with these two exceptions, once high doses of steroids were introduced, no further vision loss occurred in any of our patients. This was true even during subsequent flare-ups related to decrease of steroid dosage when symptoms of myalgia, fever, and malaise occurred and the sedimentation rate once again became elevated. This would indicate that the major risk of vision loss would be early in the course of the disease. Beevers et al (5) reported the case of a 72-year-old man who, seven months after the onset of a myalgic syndrome, developed loss of vision in one eye. The highest dose of steroids he had ever received was 30 mg a day. They report another patient, a 77-year-old woman with temporal arteritis who three years after diagnosis, developed sudden blindness in her right eye and was found to have extensive hypertensive retinopathy. At the time of blindness, her sedimentation rate was 35. In this patient, it is not certain that her vision loss was related to active arteritis.

Hart (6) describes a 75-year-old man who had a history of either polymyalgia rheumatica or rheumatoid arthritis for a period of four years and was treated with small doses of corticosteroids and indomethacin. After he had been in total remission for two years he developed fever, coryza, temporal headaches and vision loss due to presumptive cranial arteritis though no biopsy was performed.

Simkin (7) describes a patient who, three years after the onset of a myalgic syndrome for which he never received corticosteroid treatment, developed claudication of the jaw and decreased temporal artery pulsations. While awaiting biopsy, he lost vision and was found to have cranial arteritis. It should be noted that this patient never received treatment for his arteritis before blindness ensued.

Cullen (8) reported a woman who had had temporal arteritis confirmed on biopsy at the age of 64. Seven years later she developed an ischemic optic neuropathy at which time her sedimentation rate was 45. A temporal artery biopsy showed no evidence of arteritis and it was only presumed that the vision loss was related to active arteritis.

Miller (9) reported a case of a patient with temporal arteritis in whom eye complications occurred three years after diagnosis.

Thus the overall experience seems to confirm that vision complications occurring late in the course of cranial arteritis, are rare. Under the best circumstances, steroids in high doses are associated with a high incidence of side effects but elderly people in particular are prone to the ravages of steroid complications particularly osteoporosis, myopathy, exacerbation of diabetes, hypertension and congestive heart failure. In our own experience, 25 patients had serious steroid problems. Thus, taking all factors into consideration, it seems that the risk of blindness late in the course of cranial arteritis is relatively low, as compared to the almost certain steroid complications that would occur with continued use of high dose steroid treatment. Indeed, in our experience, consequences of arteritis, cranial or otherwise have been rare. And the quoted cases of late ophthalmic pathology (5−8) are not thoroughly authenticated as arteritis related.

Based on these considerations, the following is our present policy for the management of cranial arteritis:

Patients who are suspected of having cranial arteritis are immediately given 60 mg of prednisone and maintained on that as a daily dose and arrangements made for temporal artery biopsy. If the biopsy proves to be positive for arteritis and the clinical response is satisfactory, the patient is maintained on 60 mg/day for two weeks with careful clinical monitoring in terms of headache, visual disturbance, fever, malaise, and jaw claudication. The sedimentation rate is also followed. A satisfactory clinical response should be rapid and, if not, the dose of prednisone is increased to 120 mg/day. After the clinical activity has been sucessfully suppressed for two weeks, the steroids are gradually tapered at the rate of 5 to 10 mg/week until a daily dose of 20 mg/day is reached. The steroid dose continues to be decreased by 2.5 mg/week to a level of 10 mg/day. From that point on the steroids are tapered by one mg every two to four weeks. Although the sedimentation rate is followed, decisions to raise steroid dose are made primarily on clinical criteria and sedimentation rate alone is not used as the basis for increasing the steroid dose. When the "flare-up" is primarily fever, myalgia, or malaise, the steroids are increased by only 10 mg/day. If, however, the patients develop visual symptoms, the dose is increased once again to 60 mg/day. This has occurred only twice in our series, and the patients always responded to the increased dose.

The sedimentation rate by itself is not used as an indicator of active disease because of the multitude of factors in an elderly patient which can cause sedimentation rate elevation. That the sedimentation rate alone can be a poor indicator of the activity of the arteritis was demonstrated by the two patients in this series who became blind despite normal sedimentation rates and who demonstrated an active arteritis on biopsy. Furthermore, one patient who died of a coronary occlusion (due to atherosclerosis) after her arteritis had been in clinical and laboratory remission for two years, showed diffuse active arteritis on autopsy examination, though her sedimentation rate was normal.

Until there is more knowledge of the etiology and pathogenesis of cranial arteritis, the treatment will remain empiric. Further information as to the natural history of the disease is needed to further define that subgroup of patients at greatest risk of blindness and other vascular insult and the optimal dose of steroid needed for treatment.

On the basis of presently available information however, it would seem that aggressive steroid treatment be reserved for the early acute phase. Later in the disease, a more conservative approach would appear to be justified.

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Virchow-Troisier's Lymph Node as the Presenting Sign of Hepatocellular Carcinoma

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Virchow-Troisier's lymph node as the presenting sign of a clinically occult hepatocellular carcinoma (HCC) has been reported in the literature only once (1). We had the opportunity to study a patient demonstrating this phenomenon. We report the case and discuss the modern methods used in establishing the diagnosis of HCC.

Clinical History

A 73-year-old woman, with known liver cirrhosis, was admitted for evaluation of lethargy, jaundice and ascites, which had developed during the last four months. Twenty-five years previously she had undergone radical mastectomy for infiltrating small cell carcinoma of the left breast. She had received blood transfusions during the operation. The patient was known to be a chronic alcohol consumer, ingesting at least 3–4 cans of beer daily. There was no history of hepatitis. During the last six months she complained of severe back pain. On admission, her temperature was 36.8° C, the pulse rate was 88/min, and the blood pressure was 150/80 mm Hg. Physical examination revealed mild jaundice, multiple petechial and ecchymotic hemorrhages, spider angiomata on the chest and Dupuytren's contracture of the right hand. There was tense ascites. There were no signs of collateral venous circulation, and the liver and spleen were not palpable. An enlarged, hard, nontender lymph node was palpated in the left supraclavicular region (Virchow-Troisier's lymph node).

Chest x-ray showed diffuse and massive widening of the mediastinum. Scintiscan showed multiple focal defects in a normal-sized liver. Sonography demonstrated ascites, and showed diffuse thickening of the gallbladder wall, which was interpreted as being compatible with diffuse metastatic involvement. Cholangiography was attempted, but visualization could not be achieved. Laboratory studies of the blood showed: glucose, 124 mg/dl; BUN, 18 mg/dl; bilirubin, 3.4 mg/dl; glutamic oxaloacetic transaminase, 156 mU/ml; glutamic pyruvic transaminase, 105 mU/ml; alkaline phosphatase, 195 mU/ml (normal range: 30–85 mU/ml); total protein, 8.7 g/dl; albumin 2.3 g/dl; globulin, 6.0 g/dl; alpha-1-globulin, 0.4 g/dl; alpha-2-globulin, 0.8 g/dl; beta-globulin, 0.5 g/dl; gamma-globulin, 4.3 g/dl; IgG, 319 mg/dl; IgM, 220 mg/dl; IgA, 450 mg/dl; prothrombin time, 17 sec. (normal range: 12–14 sec), hemoglobin 13.1 g/dl, WBC count 8,700/mm^3, platelet count 72,000/mm^3. The alpha-fetoprotein level was 305 ng/ml (normal range: 25–50 ng/ml). Serum studies for hepatitis B surface antigen, antimitochondrial antibody, anti-smooth muscle antibody, antinuclear antibody and anti-parietal cell antibody were negative. The stools were guaiac test positive. The enlarged supraclavicular (Virchow-Troisier's) lymph node was biopsied on the tenth hospital day.

The patient's state of consciousness progressively deteriorated with a concomitant rise in her plasma ammonia level from 150 mcg/dl on admission to 290 mcg/dl twelve days later. She developed hepatic coma and bilateral bronchopneumonia, and expired two weeks after admission. At this time the site of origin of the primary tumor was not evident.

Pathologic Findings

The biopsied lymph node was gray-white, hard and 2.5 × 1.0 × 1.0 cm in maximal diameters. Histologic examination showed that most of the

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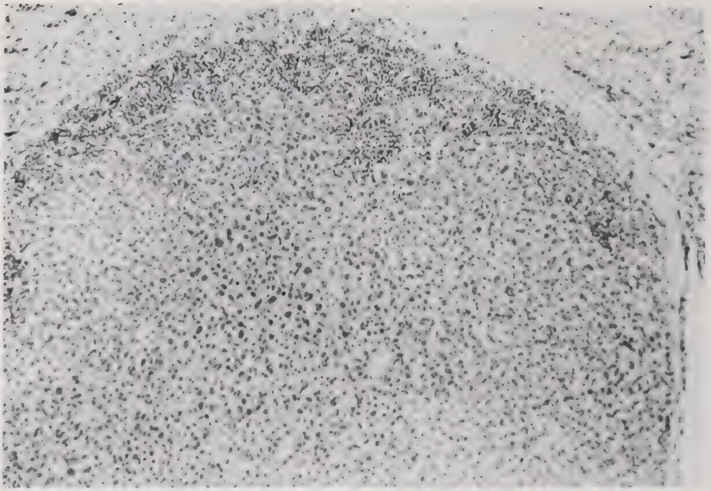

Fig. 1. Photomicrograph of surgically removed Virchow-Troisier's lymph node showing almost complete replacement of architecture by metastatic carcinoma (hematoxylin and eosin stain, original magnification ×100).

normal architecture was replaced by compact neoplastic cells, without intervening sinusoidal spaces (Fig. 1). The tumor cells showed variation in nuclear shape. No tumor giant cells, bile formation or mucin production were seen. The node was interpreted as showing metastatic poorly differentiated adenocarcinoma.

Postmortem examination revealed 4,500 ml of sanguineous ascitic fluid and multiple carcinomatous peritoneal deposits. There was bilateral confluent bronchopneumonia.

The liver weighed 1,450g, and showed regular (micronodular) cirrhosis and multiple tumor nodules in both lobes. The nodules were gray-

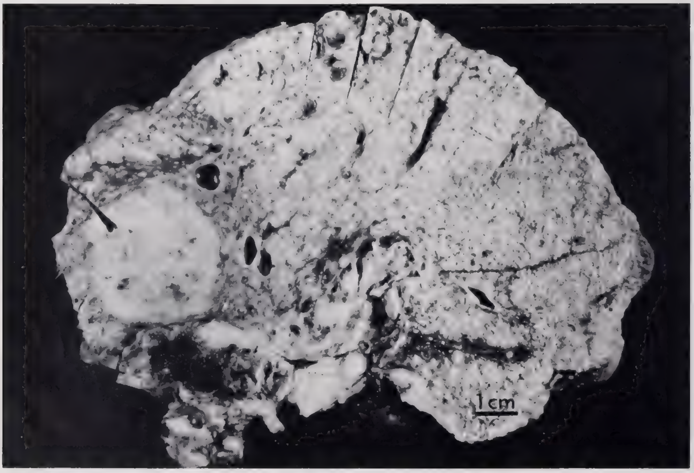

Fig. 2. Cut surface of liver at autopsy showing regular (micronodular) cirrhosis and a large tumor nodule.

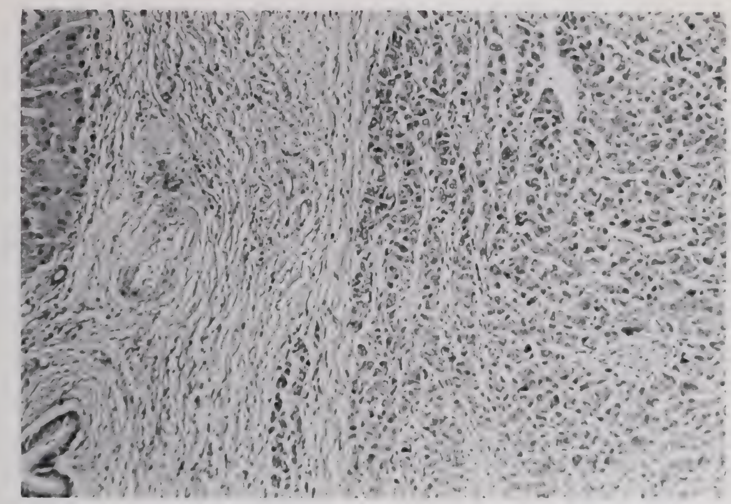

Fig. 3. Photomicrograph of HCC in liver showing trabecular pattern. Fibrous band and non-neoplastic parenchyma are shown on the left (hematoxylin and eosin stain, original magnification ×100).

white, 0.8 to 5.0cm in diameter, the larger ones with central hemorrhagic necrosis (Fig. 2). Tumor invasion of the intrahepatic branches of both the portal and hepatic veins was evident grossly. Histologic examination documented that the tumor was a multifocal HCC. In the liver, the neoplastic cells had large, vesicular nuclei with prominent nucleoli, and while in most areas the tumor showed no definite architectural pattern, in focal areas there was trabecular formation (Fig. 3) or small acinus-like clusters. Bile and mucin production were not demonstrated by use of appropriate staining techniques. The remainder of the liver showed cirrhosis with scant chronic inflammatory infiltrate in the fibrous septa. Mallory's alcoholic hyaline bodies were absent. The gallbladder wall was thickened up to 2.0 cm by confluent, gray-white tumor nodules, some showing necrosis. The bile was viscous and dark red due to hemorrhage. There were no gallstones.

The mediastinal lymph nodes were diffusely involved by metastatic tumor, and were matted together. The lymph nodes at the porta hepatis and the periaortic and peripancreatic nodes were similarly involved. The enlarged peripancreatic nodes were noted to impinge upon the spinal nerves in the intervertebral foramina of vertebrae L 1 to L 3. The cervical lymph nodes, except for the surgically excised left supraclavicular node, were spared. Small, bilateral pulmonary and pleural metastases were found. The spleen weighed 320 g, and showed fibrocongestive changes. There were esophageal varices and internal hemorrhoids.

Review of the histologic sections of the breast tumor removed twenty-five years previously confirmed the original diagnosis of infiltrating small cell carcinoma with a histologic character different from the HCC. The axillary lymph nodes in the mastectomy specimen were free of metastases.

Discussion

It is well known that left supraclavicular lymph nodes may be a site of metastatic seeding of an intra-abdominal or left-sided thoracic malignancy. This clinical finding, the Virchow-Troisier node, is most often associated with tumors of gastric origin (2, 3).

The usual presenting symptoms and signs of HCC are well recognized and documented in several reports (1, 4–7). To the best of our knowledge, this report is only the second documentation of the Virchow-Troisier node as the presenting sign of HCC (1). In four other reported patients there was diffuse spread of a previously diagnosed HCC to cervical lymph nodes (4, 6, 7). In these cases (1, 6, 7), in which cervical lymph node involvement was documented, the mediastinal nodes were spared. In one case (4), the mediastinal nodes were also involved. However, mediastinal lymph node involvement in HCC is not rare (1, 4–6). In the present patient both the left supraclavicular and the mediastinal lymph nodes were involved.

It is well documented that in its lymph node metastases, HCC may appear histologically more anaplastic than in the liver or in nonnodal metastatic locations (8, 9). This phenomenon represents a diagnostic challenge to the pathologist who examines a lymph node metastasis of an occult HCC.

Involvement of the gallbladder and guaiac test positive stools are not rare in HCC (9, 10), although frank hemobilia is infrequent (1). Of course, an increased level of alpha-fetoprotein strongly favors the diagnosis of HCC (11).

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Atypical Calcification of a Uterine Leiomyoma

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Abstract

An unusually densely calcified uterine leiomyoma is presented. Radiologic-pathologic correlation and differential diagnosis are discussed.

Calcified uterine leiomyomata are frequent radiologic findings in the female pelvis. The pattern of calcification is often characteristic and easily recognized. Recently, we have seen a leiomyoma with an unusual pattern of calcification which obscured the true nature of the lesion.

Case Report

A 40-year old black female G_2 P_{1001} presented with a six-month history of severe dysmenorrhea and menorrhagia, and a midline pelvic mass which had been present for a year. She had previously been in good health without change in bladder or bowel habits. Pelvic examination revealed a 12 to 14 week size nodular fibroid uterus. The adnexae were not palpable. Laboratory examination was remarkable only for anemia of 9.8 grams hemoglobin. Hysterosalpingography was performed to rule out a submucosal component of the uterine leiomyomata. Preliminary film revealed a 5 cm × 7.5 cm densely and homogeneously calcified ovoid mass in the right mid-pelvis (Fig. 1). Hysterosalpingography revealed the mass to be separate from the uterus, posterior, and to the right (Fig. 2).

Total abdominal hysterectomy and bilateral salpingo-oopherectomy were performed. A multifibroid uterus was found with a single large calcified intraligamentous fibroid on the right. There were, in addition, endometriomata and mature teratomata of both ovaries.

Discussion

Pathologically, leoimyomata are sharply circumscribed, unencapsulated but discreet, usually round, firm, gray-white masses that have a characteristic whorled cut surface. Histologically, the leiomyoma is composed of whorling bundles of smooth muscle cells that more or less resemble the architecture of normal myometrium (1). The deposition of calcium phosphates and carbonates in uterine leiomyomata is evidence of degenerative change associated with diminishing blood supply and necrosis. It is most often seen in elderly women, in blacks and in pedunculated subserous tumors. In one study, calcification occurred in 4.3% of myomata in blacks versus 2.4% in whites (2). Another study, of blacks only, showed calcification in 7% (3).

Degenerated leiomyomata are usually free of symptoms but occasionally cause acute abdominal pain, fever or sepsis. Calcified leiomyomata may break through the bladder or intestinal wall (4).

Leiomyomata are first detectable radiographically when they begin to calcify. The deposition of calcium may be irregular or diffuse and in varying amounts. It may be deposited at the surface of the growth at first and form a calcareous shell resembling a calcified cyst. There may be uniform coarse speckled calcifications or a very coarse honeycomb density with wavy borders (5). As a result of general necrosis, the leiomyomata may become solidly calcified, even to the consistency of ivory, termed "uterine stones" or "wombstones" (6, 7).

When a strikingly calcified mass such as this is seen in the pelvis, the major diagnostic consideration is calculus in a bladder diverticulum. Also to be considered are enterolith secondary to partial

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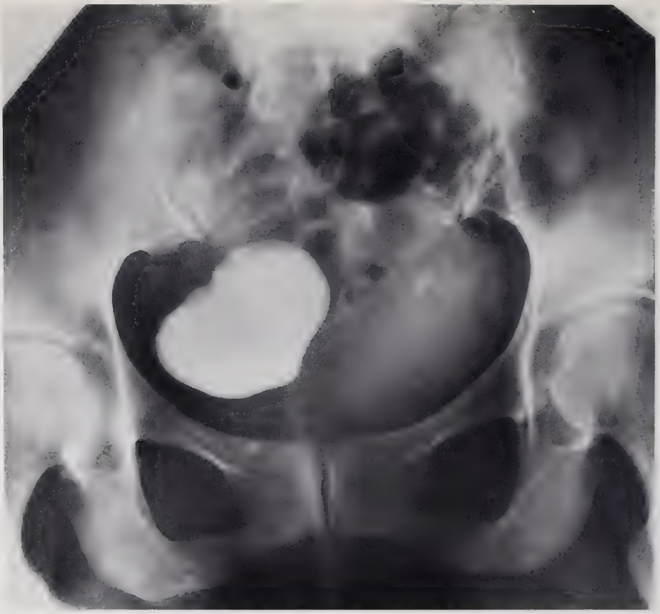

FIG. 1. Densely calcified right pelvic mass, adjacent to soft tissue mass in left pelvis.

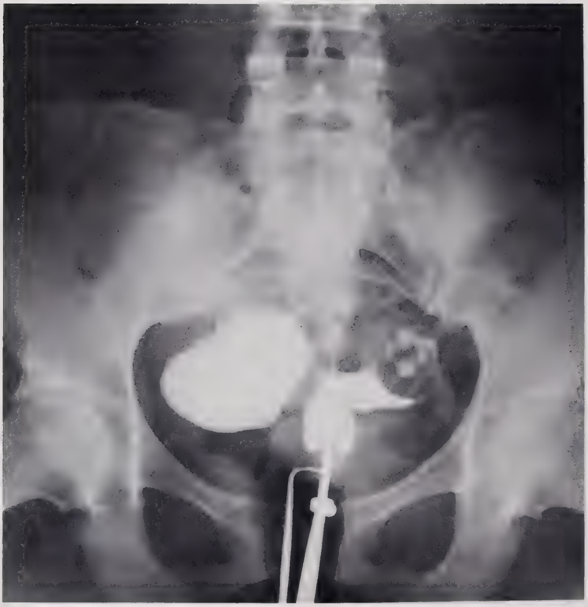

FIG. 2. Hysterosalpingogram. Calcified mass adjacent to uterus. Normal left fallopian tube; right not filled. One centimeter filling defect in uterine cavity.

bowel obstruction, enterolith in a Meckel's diverticulum, calcified leiomyoma, barium concretions in a Meckel's diverticulum or other intestinal diverticulum, gallstone in the ileum and lithopedion. A leiomyoma as densely calcified as the present example is very rare. Search of the literature did not reveal a similar lesion. Uncommon manifestations of common conditions may be more common than the reverse.

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The Klippel-Trenaunay Syndrome: A Case Report and Review of the Literature

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Abstract

The Klippel-Trenaunay syndrome is a congenital angiodysplasia which usually involves one lower extremity or a portion thereof and is characterized by varicose veins, port-wine cutaneous hemangiomas, and symmetrical hypertrophy of the affected limb. Since first described by its eponyms in 1900, more than 300 cases have been reported, mostly in the European literature (1–5). The present case report illustrates the features and complications of the syndrome.

Case Report

A 23-year-old, Egyptian male presented with an ulceration of his second right toe. He had been born with superficial varicosities involving his right lower extremity and had a history of previous perimalleolar ulcers as well as a greater saphenous vein stripping four years prior to admission in Egypt. Physical examination revealed a symmetrically enlarged right lower extremity 3.5 cm longer than the left with numerous large varicosities. Hyperpigmented venous stasis changes were noted from his toes up to the midcalf. No hemangiomas were detected, and peripheral pulses were normal. Blood sampling from his varcosities compared with his arterial blood gases suggested the presence of arteriovenous fistulae (Table I). An echocardiogram revealed mild cardiac dilatation without hypertrophy, atrial enlargement or valvular anomalies, and was thus indicative of high output failure. A normal gaited pool scan with a left ventricular ejection fraction of 68% ruled out cardiomyopathy. Therefore, the likeliest cause for his high output failure was believed to be arteriovenous shunting.

The patient was then referred for angiographic evaluation. Following percutaneous left femoral arterial catheterization, an injection of contrast material above the aortic bifurcation demonstrated symmetrical dilatation of the entire right arterial tree from the aortic bifurcation to the distal anterior tibial artery (Fig. 1). A peripheral study also showed symmetrical enlargement of the arteries of the right leg as well as multiple anomalous branches of the superficial femoral artery and early filling of numerous varicosities throughout the leg and right hemipelvis. However, no large, focal arteriovenous fistulae were observed (Fig. 2). Despite multiple rapid sequence films following the injection of a high volume of contrast material, no early draining veins were visualized. This may have been due to a dilutional effect by the unopacified blood in his voluminous vascular bed.

Discussion

Any discussion of this syndrome or its variants classically deals first with a confusion over its

TABLE I

	pO_2	pCO_2	pH	% O_2 Saturation
1. Arterial Blood Gases	101	37	7.41	97.4
2. Venous Blood Gases				
Thigh	81	38	7.41	95.4
Knee	96	34	7.45	97.4
Calf	98	37	4.43	97.4

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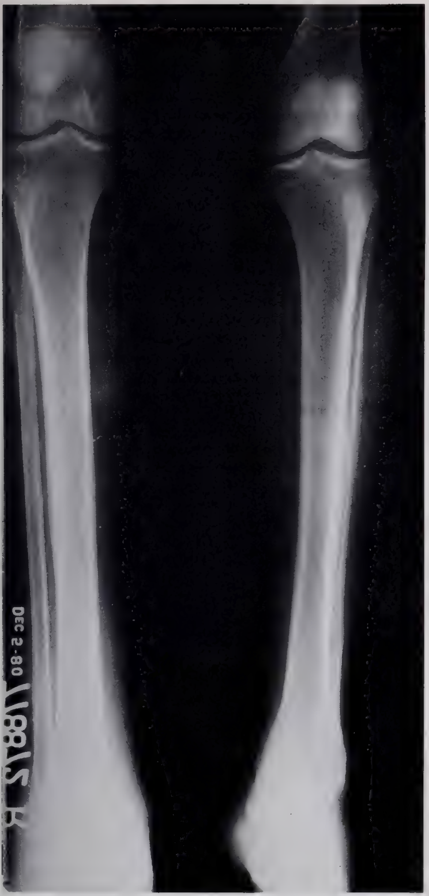

FIG. 1. Scout film of the lower extremities demonstrating the disparate leg length.

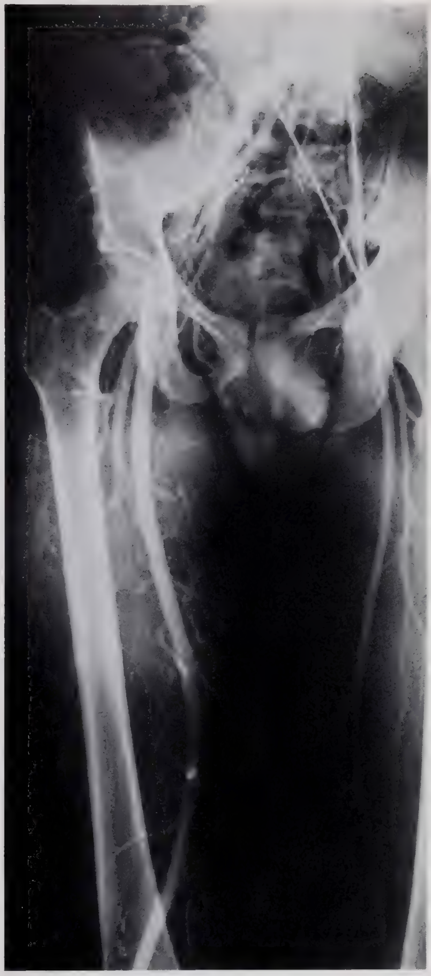

FIG. 2. Arterial angiographic phase demonstrating symmetrical dilatation of the right arterial tree with multiple anomalous branches.

nomenclature and then compounds the confusion by suggesting yet another name. In keeping with tradition, the various terminology shall be listed in passing. Parkes-Weber (6) described a syndrome in 1907 which, in addition to the Klippel-Trenaunay triad of varicosities, cutaneous hemangiomata and limb hypertrophy, also included arteriovenous fistulae. Since then, combinations of the above names have been variously used, though some attempts have been made to relegate the eponym Parkes-Weber to those cases with fistulous manifestations and designate the remainder as Klippel-Trenaunay. This distinction is semantic only up to a point, because although both entities probably share a similar pathogenesis, the presence of arteriovenous fistulae clearly worsens the prognosis by heralding the occasional high output cardiac failure. A host of descriptive terms has also been proposed for

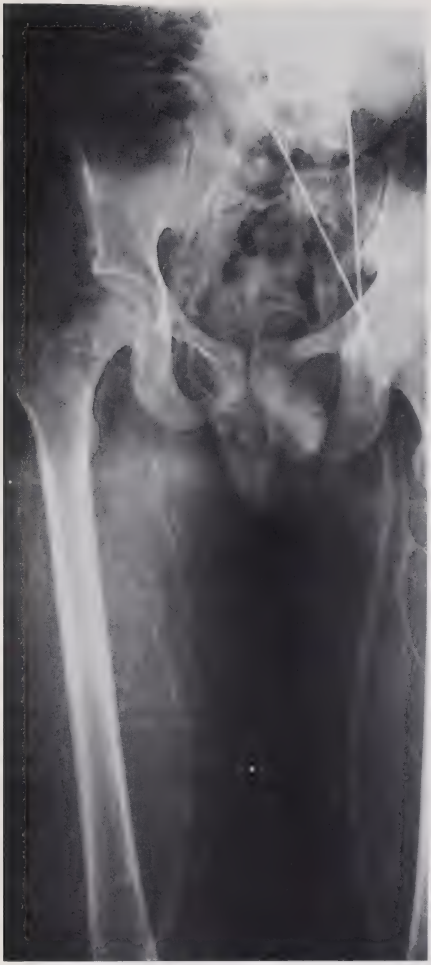

FIG. 3A Early filling of numerous varicosities in the leg and pelvis.

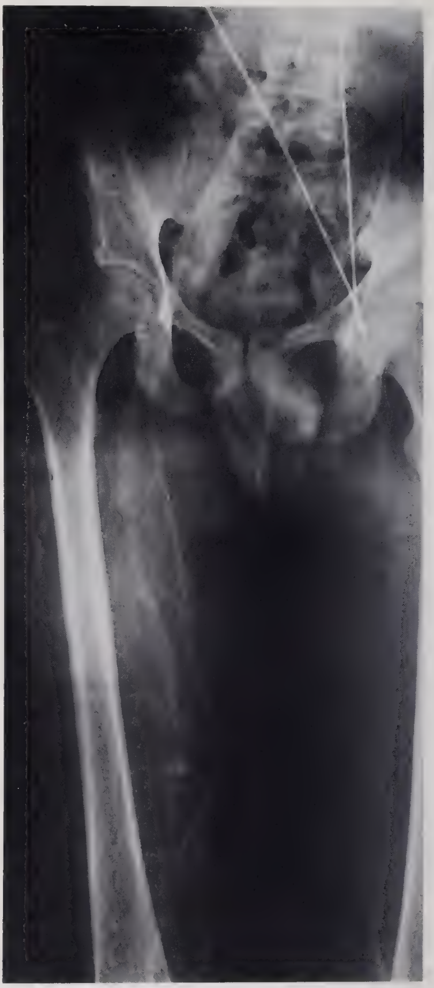

FIG. 3B Early filling of an enlarged right external iliac vein and common iliac vein while the opposite extremity is still in the late arterial phase.

this syndrome. However, since none of them has gained popularity, they shall not be here belabored. Rather, the syndrome with all its variations shall be simply referred to as Klippel-Trenaunay.

The etiology of the Klippel-Trenaunay syndrome is as yet unknown. It does not, however, appear to be hereditary, nor is there a sex preference. Associated congenital malformations have been reported, including spina bifida, pes equino varus, and poly- and syndactyly (7). Some manifestation of the disease, especially the cutaneous hemangioma, is usually present at birth. The varicosities typically appear next, particularly once the affected child has begun walking erect. The limb hypertrophy is commonly the last noticed feature of the cardinal triad. This chronology does vary occasionally, and, in fact, the triad may be incompletely represented, as in the case in point. The syndrome is usually confined to the entirety of the lower extremity. Less frequent variations involve an upper limb, two limbs, or only a portion of a limb. Extension of a lower limb lesion into the pelvis is not uncommon and may be associated with organomegaly and intestinal bleeding (5, 8−10).

The universal feature of the Klippel-Trenaunay syndrome is at least one kind of venous anomaly, the most common of which are superficial varicosities. The deep venous system is also almost always involved and may be absent, hypoplastic, or atretic at any level of the extremity or pelvis. Venous return is accommodated primarily by the dilated, valveless, superficial venous network in such cases of deep venous compromise. The presence of varicose ulcers, dyskeratosis, and edema appears directly related to the degree of venous stasis. Venous return via an enlarged superficial, anomalous vein has also been reported (5). The superficial and deep systems may be extensively filled with thrombus, although pulmonary emboli are paradoxically not a feature of the disease (9). Failure to visualize the deep veins phlebographically has also been ascribed to the use of an insufficient volume of contrast material. Supplemental injection sites, such as the pericalcaneal and peritrochanteric areas as well as direct injection into a superficial varix, have been recommended when pedal injection alone fails to demonstrate the deep veins (11, 12).

The characteristic limb hypertrophy includes enlargement of all tissue layers. Accordingly, the increased limb circumference is usually proportional to the increased limb length. Increased arterial perfusion secondary to hemangiomatosis and heightened venous capacitance is thought to account for the hypertrophic changes (9).

Arteriography often demonstrates a normal or nearly normal arterial phase. Alternatively, multiple aberrant branches of the arterial arcade are frequently observed, as in the superficial femoral artery of the present case. This case also illustrated a less common feature, namely a diffusely symmetrically dilated arterial tree. Since the arteriovenous fistulae, when present, tend to be innumerable and microscopic, arteriography rarely provides a direct testament of their existence. Indirect evidence consists of abnormally early venous filling, a dilatation of the afferent arteries and augmented venous oxygen pressure (5, 8).

Less common associated manifestations of the syndrome include lymphatic dysplasias of the affected extremity, such as hypo- or hyperplasia of the lymph vessels and cutaneous lymphangiomata. The frequency of deep lymphatic involvement is currently inestimable, however, because lymphography has been seldom performed in these cases. Rare features include facial hemihypertrophy (13), varicose pulmonary veins (14), and hypoplasia of the affected extremity (5, 8).

The prognosis is generally favorable with the exception, as mentioned above, of cases with extensive arteriovenous shunting. The progression of the disease usually ceases in the late second or early third decade. Accordingly, treatment in uncomplicated cases has typically been limited to leg elevation and use of compression stockings. When indicated, epiphysiodesis or a shortening osteotomy may be employed. Venous stripping has been notoriously unsuccessful due to the resultant augmentation of venous stasis, the recurrence of the varicosities, and the not uncommonly insufficient deep venous system. Furthermore, surgery short of amputation is often rendered impossible by the extent of the lesion (8, 9, 15). Amputation has been used in desperation in cases of overt heart failure.

Recent attention has been given to percutaneous transcatheter selective embolization. Two cases thus treated by Joyce et al met with reportedly good results in a 1½ and 4 year follow-up, respectively (16).

It would seem that transcatheter embolization of Klippel-Trenaunnay lesions may prove to be a hopeful alternative to amputation, but that it should be guardedly approached until thorough and long-term studies have been accomplished.

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Cholecystectomy in Patients Above 70: Review of 153 Cases

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Abstract

Advances in surgery and anesthesia have revolutionized the surgical care of the biliary tract in the geriatric age group. This report deals with 153 patients aged 70 and over, and with a series of 1000 consecutive cholecystectomies. All data were computer analyzed. The following principles were used:

1. Early surgery was performed within 48 hours after full diagnostic investigation and adequate preparation in all patients with acute or subacute complications.
2. One stage definitive procedure including cholecystectomy, operative cholangiography, and complete correction of pathology in the common bile duct were preferred to temporary measures such as cholecystostomies.
3. Careful anesthesia management before, during, and after surgery.

The mortality in this series was 2.6% only, considerably lower than other reported series in this age group.

Complicating factors, such as infected bile, jaundice, choledochal stones and gangrenous changes are much more frequent in elderly patients than in other groups.

The principles outlined combining early surgery, complete correction of biliary pathology, and intensive postoperative care whenever needed, have resulted in dramatic reduction of mortality and morbidity in the elderly patient.

Biliary tract disease has become the most common condition requiring major abdominal surgery in the elderly patient. This fact is not surprising since it is estimated that more than 50% of patients aged 70 and above harbor gallstones in the biliary tract (1). The incidence of serious complications in this age group is much higher than in the young. Strohl reported that 75% of abdominal emergencies encountered in the elderly were related to the biliary tract (2).

The treatment approach to elderly patients has been controversial. While some authors have advocated early surgical treatment, all too often these patients are either treated conservatively or surgery is delayed and, when performed, inadequate.

Many advances have been made in the last two decades in the preoperative, operative and postoperative treatment of surgical patients. These advances include modern anesthetic methods, the proper use of antibiotics and blood, and the use of specialized intensive care units for patients who need them.

These improvements in the fields of surgery and anesthesia have revolutionized the surgical care of the elderly patient, and prompted us to revise the traditional attitude towards surgical indications and tactics in biliary surgery.

The surgical policy applied in this series differs considerably from that which is usually applied to geriatric patients. The principles can be summarized as follows:

1. Early surgery performed within 48 hours after full diagnostic investigation and adequate preparation in all patients with acute or subacute complications.
2. One stage definitive procedure including cholecystectomy, operative cholangiography, and complete correction of pathology in the common bile duct are preferred to temporary measures such as cholecystostomies.

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The safe and successful management of anesthesia in biliary tract surgery of the elderly was based on the following principles:

a. Thorough preoperative assessment and management.
b. Correct selection of anesthetic technique and drugs which will provide the best possible operative conditions for the surgeon and at the same time disturb as little as possible the cardiovascular and respiratory stability of the patient.
c. Constant monitoring of vital functions throughout and after surgery.
d. Aggressive postoperative care.

The purpose of this study is to evaluate the surgical and anesthetic approach to biliary tract disease in the elderly patient as used in this series and to compare it with other published results. In addition, the special features of biliary tract disease and biliary tract surgery in the elderly have been studied and compared to the same features in younger patients.

Materials and Methods

All patients undergoing cholecystectomy for benign disease of the biliary tract were included in this study. The total number of cases studied were 1000, of which 153 were aged 70 and over, 847 were aged 69 years or less. Both elective and emergency procedures were included. The data was collected and analyzed using a computer Data General Type Nova 2.

There was a predominance of female patients (Table I), however this was much less pronounced than in the younger age group. Almost half the patients (Table I) were operated upon during the acute stage of their disease, acute inflammatory changes being confirmed by pathologic examination. Twenty-one of the patients with acute cholecystitis showed gangrenous changes and one had a perforation. Jaundice (bilirubin above 2 mg) was present in about one fourth of the cases, and at least one major complication was present in about two thirds of the cases (Table I). Only about one third of the cases could be described as elective, practically all of these were either symptomatic or incidental (during unrelated procedures).

Operative cholangiography was performed in practically all the cases via the cystic duct (Table II) and the number of stones in the gall bladder and bile duct, and the size of the choledochus were carefully recorded in all cases. Bile cultures and sensitivity were obtained in all cases from the gall bladder and wounds were cultured in all postoperative wound infections as well as other septic complications. A comprehensive preoperative investigation was an important part of the anaesthetic management.

TABLE I
Cholecystectomy in Patients above 70

153 out of 1000 consecutive cholecystectomies (15.3%)

Males	63	F:M ratio = 1.4:1
Females	90	

	Cases	%
Acute Cholecystitis	64	42
Jaundice	43	28
Pancreatitis	14	9
Elective cases (none of the above present)	53	34

TABLE II
Operative Findings and Procedures

	Cases	%
Operative cholangiography	149	97
Choledochal exploration	68	44
Stones	53	35
Fibrosis or stricture	6	4
Negative exploration	9	6
Choledochoduodenostomy	21	14

Cardiovascular and pulmonary function were carefully assessed. Conditions such as heart failure, arrythmias or hypertension, if present, were treated adequately before surgery was undertaken.

The presence of preoperative pulmonary disease, especially with excessive secretions, was treated by physiotherapy, antibiotics and the cessation of smoking before the patient came to surgery, in elective cases.

The method of anesthesia consisted of the following sequence: Induction was with droperidol and fentanyl followed by diazepam or thiopentone intravenously; intubation of the trachea was facilitated by succinylcholine or pancuronium bromide and anesthesia was maintained by the inhalation of nitrous oxide and oxygen (5:3) with intermittent intravenous injections of fentanyl.

Muscle relaxation was maintained by intermittent pancuronium intravenously with intermittent positive pressure ventilation.

All patients remained in the postoperative recovery room until fully awake and until the condition was considered stable. Blood pressure, pulse, tidal volume and minute volume were measured at regular intervals and recorded. The Peak Flow Rate was measured at least once before the patient was returned to the ward. Blood gases and pH were measured by the IL Blood Gas Analyzer whenever clinical observations indicated further investigation. Postoperative pain was effectively dealt with in most cases by a mixture of 25 mg demerol with 25 mg promethazine intramuscularly. All cases received added oxygen by means of a Ventimask.

Physiotherapy, consisting of deep breathing and encouragement to cough was carried out routinely by a physiotherapist as soon as the patient was sufficiently capable of cooperating.

Any case that did not meet with the standard criteria of stability or because of the initial severity of the illness, was transferred to the adjacent Surgical Intensive Care Unit for further observation and treatment until the condition warranted transfer to the surgical ward.

Results

Choledochal exploration was performed in 44% of the cases. In only nine of the cases performed was the exploration negative. (Table II).

In about one third of the cases explored (Table II), a permanent drainage procedure was considered necessary. The indication for such a procedure was as described by our authors (3, 4). The most frequent being multiple choledochal stones or stricture in the papillary area. Choledochoduodenostomy, at least 15 mm wide, was preferred in most cases. The bile culture was positive in about 40% of specimens sampled from the gall bladder. In four out of five, gram-negative bacteria were cultured, the most frequent being E. coli (Table III), and Klebsiella. Gentamicin was by-far the most effective antibiotic, as indicated by sensitivity of bacterial strains obtained from the gall bladder bile in this series.

There were no operating room fatalities or other deaths that seemed directly attributable to anesthetic technique. Four patients in this series died during the postoperative period (Table IV), three belonged to the emergency group, one to the elective group. Pulmonary complications were responsible for two of the mortalities, sepsis and gastrointestinal bleeding was considered to be the cause of one, and acute myocardial infarction for another (Table IV).

About 20% of the patients displayed postoperative complications. The most frequent were wound infections and respiratory complications. None of the wound infections were considered to be life-threatening. The bacteria in most of the cases with positive cultures from infections were identical to strains from gall bladder bile.

TABLE III

Bile Cultures and Sensitivities

Positive Cultures 66 cases (43%)	
I. *Type of Bacteria Cultured* (% of positive cultures)	
E. Coli	67%
Klebsiella sp.	8%
Misc. Gram negative bacilli	14%
Salmonella	3%
Anaerobic species	3%
Others	5%
II. *Antibiotic Sensitivity* (% of positive strains)	
Chloramphenicol	71%
Cephalothin	65%
Gentamicin	86%
Ampicillin	45%

TABLE IV

I. *Mortality*	4 cases	F – 71 Cirrhosis, Pulmonary Embolism		
	2.6%	M – 72 Sepsis		
		F – 78 Broncho Pneumonia		
		M – 83 Acute M.I.		
			Cases	%
II *Morbidity*	Wound Infection		19	12
	Respiratory Complications		14	9
	Dehiscence		4	3
	Cardio Vascular		6	4
	Misc.		4	3
III *Follow-up*	Residual stones		4 cases	2.6
	—2 Re-operations			
	—2 Endoscopic papillotomy			
	Recurrent jaundice Cholangitis or strictures		0 cases	—

The average hospitalization period of patients without complications was eight days. A total of four cases were discovered to have residual pathology in the biliary tract (Table V).

Follow-up ranging from one to five years was obtained in all surviving patients. Most of the clinical follow-ups included filling out a detailed questionnaire. Patients displaying symptoms suggestive of recurrent disease were hospitalized and studied by appropriate techniques including intravenous cholangiography, endoscopic retrograde cholangiography, and pancreatography whenever indicated.

There were four patients with residual stones, two of the four cases required re-operation while two underwent successful endoscopic papillotomy and nonoperative removal of stones.

TABLE V

Comparative Data in Patients Above and Below 70

	ABOVE 70 153 CASES	BELOW 70 847 CASES
Clinical Data		
F:M ratio	1.4:1	3.5:1
Acute Cholecystitis	42%	24%
Jaundice	28%	10%
Elective	34%	78%
Operative Data		
Rate of CBD explorations	44%	19%
Rate of CBD stones	35%	13%
Rate of positive bile cultures	43%	21%
Postoperative Data		
Mortality	2.6%	0.24%
Wound infections	12%	8%
Respiratory complications	9%	5%

Discussion

The important conclusions to be drawn from this study are the remarkable differences between biliary tract disease below and above the age of 70.

In biliary tract surgery of elderly patients, almost 75% of the cases present for surgery with at least one acute or subacute complication as opposed to only a 33% in the younger patients.

The rate of choledochal pathology encountered is three times as high in the elderly as in the younger patient, as is the rate of positive bile cultures (43%).

This high rate of serious complicating factors, all potentially lethal in the elderly, are a strong argument in favor of early surgery. It seems that the good results obtained in this series were largely due to the fact that practically all patients with acute cholecystitis, acute or subacute cholangitis and jaundice were operated upon within 48 hours of admission to the surgical department.

One of the arguments raised against early surgery has been the high incidence of diagnostic errors. It seems to us that modern techniques such as ultrasonography and endoscopic retrograde cholangiography, and pancreatography, in addition to the ordinary visualization techniques, render this argument almost obsolete.

No instances of mistaken diagnosis of biliary pathology occurred in this series.

Cholecystostomy traditionally occupied an important place in the treatment of acute cholecystitis in the elderly patient.

There are very important reasons for abandoning this procedure which is still recommended by some specialists in the field (5). Among the most important reasons are:

1. Gangrenous changes and possible covered perforations are left behind.
2. Purulent material present in the common bile duct is usually not drained via the cholecystostomy and remains a focus of serious septic complications.
3. The need for additional surgical procedures adds to the mortality, morbidity, and economic expenses.

A problem situation for the surgeon is the elderly patient with so-called "silent gall stones" discovered incidentally.

While the condition of the patient and his desire for surgery are important, as a general policy we have not recommended elective cholecystectomy for elderly patients harboring truly asymptomatic gallstones.

Studies related to the subject indicate that about 50% of the patients will become symptomatic and require surgery during a ten-year period; others will remain asymptomatic.

The computation of cost and risk of the operative and nonoperative approach to "silent gall stones" in patients above the age of 70, favors the nonoperative approach for both medical and economic reasons.

As to "silent gall stones" in the younger age group, operative policy has a slight advantage over the nonsurgical approach. Concerning incidental cholecystectomy in patients undergoing abdominal procedures for unrelated reasons, we have favored removal of the stone containing gall bladder because of the considerable risk of complications during the immediate postoperative period.

Five patients in this group had an incidental cholecystectomy of this type, without mortality or morbidity that could be related to this procedure.

Overall, low mortality of 3% in this series in which definitive procedures were performed in all cases, speaks strongly in favor of this approach.

Routine operative cholangiography is advised by the authors in all biliary surgery. This procedure is particularly important in elderly patients because of the increased incidence of common bile duct pathology in the group. The low rate of negative explorations and residual stones in this series seems the direct result of this policy.

The technique of neurolepatanesthesia used in this series is very well suited to poor risk elderly patients undergoing surgery of the biliary tract. In a study we undertook comparing this technique with the method using halothane as the anesthetic agent, it was shown that the halothane group of patients had a greater fall in PaO_2 and a greater rise in the intrapulmonary shunt during anesthesia. There was also a 13% fall of intraoperative blood pressure with halothane and no significant change in blood pressure with neuroleptanaesthesia.

The peak flow rate 15 min after the procedure was considerably better in the neuroleptanesthesia group. It would thus appear that in biliary surgery in elderly patients, pulmonary and cardiovascular stability are more likely to be obtained with neuroleptanesthesia. When used in poor risk patients, this contributes to the low mortality and morbidity of the entire group.

The new developments in modern surgery and anesthesia render the re-evaluation of surgical results and data essential. Judging by mortality, morbidity and long-term results obtained in this series, the therapeutic policy in biliary tract disease in the Geriatric group should be based on the principles outlined, namely early surgery for acute and subacute complications and complete and definitive surgery during the primary procedure.

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A Case of Predominantly Unilateral Pseudoprimary Hyperaldosteronism

Milton Mendlowitz, M.D.

Abstract

A second case of predominantly unilateral adrenal cortical hyperplasia with pseudoprimary hyperaldosteronism and hypertension is presented, successfully managed by unilateral adrenalectomy and diuretics. This patient also had incidental early chronic lymphocytic leukemia requiring no specific therapy.

Primary hyperaldosteronism due to adrenal cortical hyperplasia is usually bilateral and the associated hypertension is unresponsive to surgical ablation. It has therefore earned the name of pseudoprimary hyperaldosteronism (1). In 1965, Ross (2), however, described one case of such hyperaldosteronism which was predominantly unilateral. The hypertension and metabolic abnormalities in this case did respond to unilateral adrenalectomy, although there was some evidence of recrudescence of the hyperaldosteronism two years later in that case. Also, Ross's patient had evidence of decreased renal function manifested by azotemia. It is the purpose of this paper to present a second similar case without azotemia, but with incidental chronic lymphocytic leukemia.

Case Report

I.H., a 57-year-old male accountant, was referred by another physician in 1973 because of failure to control his hypertension under a variety of drug regimens. The patient stated that he had known hypertension for 15 years which was largely asymptomatic. He had been a heavy smoker, but had stopped in 1963. Many drug treatments had been tried by several physicians, with little if any effect on the hypertension. There were no symptoms of alkalosis. He did, however, have nocturia two to four times a night. His usual blood pressure was 240/130 and antihypertensive medications often made his hands "feel weak."

On physical examination, there was a systolic murmur at the apex and base of 1/4 intensity. His blood pressure was 240/140. No epigastric bruit was heard and there were no other significant findings. Chest-x-ray revealed minimal left ventricular enlargement. Routine urinalysis was normal and erythrocyte sedimentation rate was also normal. The electrocardiogram showed nonspecific changes, including T_1 lower than T_3 and T inverted and ST depressed in V_5 and V_6. There was no left axis deviation but a small Q was seen in lead 3. The blood tests were all normal except that serum potassium was 2.5 meq/l and the WBC was 15,000 per cu mm with a preponderance of lymphocytes in the differential count. Repetition of the serum electrolyte analysis revealed chloride of 96 meq/l CO_2 37.5 meq/l sodium 145 meq/l and potassium 2.9 meq/l. Thus, there was a mild alkalosis with a very low serum potassium in a patient on no medication. Urinary metanephrines were normal.

The plasma renin activity was then determined (3) and found to be so low as to be unmeasurable, (0.00). The patient was then given spironolactone up to 100 mgs b.i.d. and the blood pressure was decreased to as low as 170/90, although at times it was as high as 180/110. He was hospitalized in 1974 after being off all medication for ten days. His blood pressure in hospital was 200/115 and the WBC count was confirmed to be elevated by the hematologist, with increased lymphocytes in the differential count. The hemoglobin and red cell count were normal and bone marrow aspiration confirmed the diagnosis of chronic lymphocytic leukemia in its earliest stage. The hematol-

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ogist recommended withholding all specific hematologic therapy at that time.

The serum potassium in hospital was as low as 3.1 meq/l and the urinary electrolyte excretion in 24 hours was potassium 78, sodium 136 and chlorides 166 meq.

In the radiology department, the left femoral vein was catheterized and phlebograms obtained of both adrenal veins (4). Before phlebography adrenal vein blood was obtained for cortisol and aldosterone analysis. The left adrenal gland was larger than the right and the curving of the venous pattern suggested the presence of an adenoma. Plasma aldosterone (5) was 1139 on the left and 283 ng/dl on the right (normal up to 100). The inferior vena caval aldosterone was 69 ngs/dl (normal up to 15). Plasma cortisol was 88 mcg/dl on the left and 81 mcg/dl on the right. Inferior vena caval cortisol was 12 mcg/dl.

The patient was operated upon in 1974 and after resecting the left twelfth rib the left adrenal gland was ablated. The surgeon removed what he thought was a lymph node which was later reported to be a collection of nerve ganglia. The pathologic report of the adrenal gland was "nodular cortical hyperplasia."

The postoperative course was uneventful except for a left pleural effusion which was gradually absorbed. The immediate postoperative blood pressure varied from 140/80 to 215/130 and the patient was given spironolactone from 25 mgs a day to 25 mgs b.i.d. The blood pressure gradually decreased over two years to 140/90 and on 50 mgs spironolactone b.i.d., to 130/80 in 1977. Because of breast tenderness, however, spironolactone was discontinued and 40 mgs furosemide b.i.d. substituted. The blood pressure in 1980 was as low as 120/85. All his blood chemistries had reverted to normal and his electrocardiogram was now normal, except for a small Q_3 and an inverted T_3. The systolic murmur remained unchanged. Because of an elevated uric acid caused by the furosemide, he was given 100 mgs allopurinol b.i.d. following which the uric acid became normal. His furosemide was increased to 60 mgs in the morning and 40 mgs in the evening to control his blood pressure better. The chronic lymphocytic leukemia was stable. In 1977, the ophthalmologist reported the presence of Fuch's corneal dystrophy (6) which remained unchanged over the years. Incidentally, the retina was initially reported to reveal Grade II retinopathy with arteriovenous nicking, all of which remained unchanged. His final blood pressure in 1980 was 120/80 and there was no evidence of recrudescence of his former hyperaldosteronism. Blood chemistries were all within normal limits.

Discussion

This is the second reported case of predominantly unilateral pseudoprimary hyperaldosteronism successfully managed by unilateral adrenalectomy supplemented by diuretic therapy. The only clue to the diagnosis was the failure of the predominantly unilateral nodular hyperplasia to suppress contralateral aldosterone secretion to below normal levels. Radioisotope labelled cholesterol was not available at the time this patient was first seen, but could conceivably distinguish hypertrophy from adenoma despite the large amount of radiation needed for such a study.

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Student's Corner

Lawrence Eichenfield, B.A.

Dilemmas in the Management of Carcinoma-in-Situ of the Urinary Bladder

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Carcinoma of the urinary bladder causes a significant amount of the morbidity and mortality from cancer in the U.S. today. It has been estimated by the American Cancer Society that 35,500 new cases of bladder cancer will be seen in 1980, 73% of which will be in men (1).

The proposed etiologies of cancer of the bladder are extremely varied. Several factors that have been implicated include artificial dietary sweeteners, tobacco, coffee, Schistosoma haematobium infection, as well as numerous occupational hazards (2).

There are three major types of cancer of the bladder. This paper will be concerned mainly with Transitional Cell Carcinoma since it comprises the vast majority of bladder tumors in North America. Also found are Squamous Cell Carcinoma, most commonly associated with schistosoma infestation of the bladder, and Adenocarcinoma. Both of these types have a much poorer prognosis than Transitional Cell and as such, management of these tumors tends to be of a more radical nature.

This paper will deal with Transitional Cell Carcinoma, a condition that has received growing attention since 1952 when Melicow first documented an association between carcinoma-in-situ and invasive tumors of the bladder (3). Carcinoma-in-situ is defined as "flat areas of epithelium composed of cells with anaplastic features and a disorderly pattern of growth" (4). Implicit in this definition is that Carcinoma-in-situ does not penetrate the lamina propria. This group of flat lesions is distinct from the papillomas. CIS is generally found to be a Grade III or IV lesion, containing many mitotic figures and marked nuclear abnormalities. Stage A carcinoma includes those lesions that penetrate into the submucosa but do not invade the muscle of the wall of the bladder. Most of the data available pertains to the combination of O and A lesions, and as such all figures quoted in this paper refer to all superficial carcinomas unless otherwise noted.

Urologic surgeons usually feel compelled to defer aggressive treatment such as cystectomy until muscle invasion is documented. However, once deep muscle involvement occurs, at least 50% of the patients will be dead within 18 months, and only 20% will survive five years (5). The amount of time permitted for the surgeon to save such a patient from frank invasion once the muscle is involved remains relatively brief when compared with the protracted course of the disease while the malignancy is confined to the epithelium. Farrow in 1976 found an average of 32 months of irritative bladder symptoms before any cytologic abnormalities could be detected (6). However, once invasion occurs bladder cancer metastisizes quickly, as evidenced by the absence of late appearing metastases after surgical extirpation, as opposed to breast or prostate cancer in which distant metastases may arise much later. This underlies the importance of early diagnosis and rapid treatment of this disease.

It has been stated that carcinoma of the bladder has a multiplicity of proposed etiologies. Correspondingly, there is evidence that bladder cancer is not a homogeneous entity, but may represent different subsets of malignancies, each with different behavioral prognoses, and thus the need for differing degrees of aggressiveness in treatment. Furthermore, carcinoma of the urothelium demonstrates both a very high rate of recurrence as well as frequent multifocal presentation. It has been estimated that 10% of initially diagnosed lesions are multifocal (2), and 75%–85% of superficial tumors will develop recurrences (5) with CIS recurring 85% of the time within five years. A Mayo Clinic study of 62 cases of CIS treated with transurethral resection of the bladder (TURB) showed 85% of those that developed recurrences to appear in the first year, with 60% appearing by six months, and 30% recurring within the first three months following diagnosis. After five years, 60% of the original 62 cases of CIS had invasion of the muscle with 24 patients dying of the disease (7). Additional studies have shown that neither tumor grade, number, stage, size or any combination of these parameters could accurately predict CIS recurrence (8). This high rate of recurrence still leaves 15% of CIS lesions that do not advance to invasive disease. This significant body of patients would not be best served by radical treatment. These factors point to the need to better characterize each new case of CIS in order to clarify what definitive treatment is required for each new individual case identified.

It has generally been found in tumor behavior studies that the less differentiated, higher grade lesions are associated with a greater potential for invasive growth, often with CIS as the earliest detectable abnormality. This has been determined from observations on CIS in other organs, particularly the uterine cervix (4). However, this generalization may not apply to the special case of CIS of the urinary bladder. CIS of the bladder is usually a high grade lesion histologically, although it may not always be aggressively invasive (4). Additionally, the morphology of CIS has frequently been shown to be of a more anaplastic nature than that of solid tumors residing within the same urinary bladder. Furthermore, CIS often does not spread to consume the normal bladder epithelium despite a rapid rate of cellular proliferation, but may remain self contained for years. Thus, the presence of CIS may not always herald invasive disease.

Explanations for these paradoxically anaplastic yet nonaggressive lesions include views that claim quiescent CIS may represent cell lines where some mutation has developed which has resulted in the loss of the required cellular or metabolic machinery to complete the process of neoplastic transformation. This contention is supported by the observations that the histologic changes noted in CIS are largely nuclear. Thus, some CIS's may represent altered areas of mucosa that contain many of the features of malignant epithelium that have lost their invasive potential (9).

The inability to precisely predict the clinical course and prognosis in the case of CIS presents a grave dilemma in the choice of the proper treatment, especially in younger patients. The challenge that is faced, then, is to discover what distinguishes the CIS that will quickly advance to invasive disease, usually termed Stage O, from those true CIS lesions which will remain quiescent and slowly if ever progress to a more infiltrative state.

Current recommendations for therapy of CIS include a compromise "wait a little while and see" attitude whereby those lesions which are highly symptomatic are recommended to first undergo a six month intravesical chemotherapeutic trial period, which if not definitively successful are referred for radical cystectomy. The other major approach involves those patients who are largely asymptomatic, or are picked up by urinary cytology only, which is the most sensitive test for the early detection of bladder cancer. This group is recommended to undergo a 12-month course of unsuccessful chemotherapy before conservative treatment is abandoned.

Tests which show promise in helping to differentiate the invasive Stage O lesion from the true quiescent CIS include the Specific Red Cell Adherence Test which takes advantage of the fact that most neoplastic urothelial cells lose their ABH blood group isoantigens as part of the malignant dedifferntiation process. This allows malignacies to be identified by red blood cell ABO antigen binding assays. This test has an additional advantage in the availability of capillary endothelium cells within biopsy specimens for use as an endogenous control (10–12). Studies of material from cystectomy specimens showed a high correlation between invasiveness and loss of ABH isoantigens. Normal mucosal cells in the bladder remain positive for RBC binding, and a positive binding of tumor cells indicates a good prognosis, that is, a lower potential for invasion. This test has the additional advantage of being inexpensive, uncomplicated, and requires no special equipment.

An additional test being studied concerns chromosomal evaluations. The presence of a ring chromosome or the A-1 chromosome was found in 90% of those CIS lesions which recurred. These markers were absent in the remaining 10% of lesions which eventually recurred (13).

Good results have also been found in studies concerning the urinary fibrinogen degradation products levels, carcino-embryonic antigen (CEA) blood levels, and immunologic skin reactivity tests with solubilized tumor antigens (2).

Until more reliable prognostic indicators are available, however, patients will have to continue to be monitored by periodic urinary cytology and cystoscopy with random biopsies, and the treatment protocol for each individual case of carcinoma-in-situ of the urinary bladder will have to be determined on a highly individual basis.

Treatment

Conservative management is most often elected when carcinoma-in-situ is encountered. Transurethral local excision and/or fulguration is a safe procedure that does not hinder bladder or sexual function and can be safely repeated. Transurethral resection is most effective against visible lesions that are less than 5 cm in diameter, well delineated, and are not located in the bladder neck, urethra, or ureteral orifice in ABH positive patients who are not severely symptomatic. However, CIS is often a diffuse disease which may not be visible through the cystoscope. Additionally, when visible, CIS may be very difficult to differentiate from certain inflammatory areas. Commonly indistinct CIS borders potentiate the possibility for failure to destroy all cancer present, together with the alternate problem of "seeding" of tumor cells onto exposed muscle. These factors tend to allow a very high rate of recurrence of these lesions, and the recommendations for follow-up include repeat cystoscopy with multiple random biopsies every three months.

Advances in TURB include experimentation with lasers, whereby the resected tumor bed is irradiated to ensure more complete destruction of malignant cells. This procedure is very expensive, but Staehler and associates have reported good results (14).

Urinary cytology remains as the best monitor of carcinoma of the bladder. Advances in flow cytometry, whereby acridine orange dye, which is preferentially absorbed by some tumor cells is applied to bladder washings, may further facilitate cytologic diagnosis. Additionally, tetracycline fluorescence methods are currently in practice in the U.S.

The best results from TURB have been achieved when this procedure is combined with chemotherapy. Intravesical chemotheraputic agents for the treatment of carcinoma of the bladder have been used since 1953 when Thiotepa was first introduced (15). Intravesical instillation of an isotonic solution of an alkylating agent allows for a high concentration of the drug to reach the malignant cells with minimal systemic side effects. Important systemic reactions that do occur include myelosuppression, which remains relatively rare since most of the drug cannot be absorbed from the bladder. Local effects largely involve irritative bladder symptoms.

Thiotepa is the most commonly used intravesical chemotheraputic agent in the U.S. Thiotepa instillation has been shown to destroy about one third of superficial tumors, reduce an additional third, and have no effect on the remaining third of superficial lesions treated (15, 16). The value of Thiotepa in prophylaxis is as yet unproven (17).

Epodyl is a chemotheraputic agent which is used more commonly in Great Britian. Robinson and associates (15) have followed 51 patients and have reported similar results as those obtained with Thiotepa in the U.S.

Mitomycin C has been promoted as an agent that produces fewer systemic side effects than Thiotepa. The basis of this claim is that it is absorbed from the bladder to a lesser degree than Thiotepa since it has a higher molecular weight. Mishna (4) found 44% of superficial tumors he exposed to Mitomycin C to be destroyed, 32% partially affected, and 24% of superficial tumors to have been left unchanged.

The current literature concerning Adriamycin (Doxorubicin) contains several highly successful reports on a minimum number of patients. Edsmyr (15) reported seven of eight patients with CIS to have lost all cytologic evidence of disease in 1979, and then followed up that report in 1980 stating cytologic remission in all 11 patients with CIS in his study (19). Uyama (20) and Jaske (21) have reported somewhat less successful results with Adriamycin in patients with CIS this year.

Other conservative measures include radiation therapy which is often selected by young male patients who refuse the sexually crippling cystectomy procedures. Radiation therapy alone has not been shown to be significantly effective in combating carcinoma of the bladder. Quite to the contrary, radiation therapy has often increased irritative complaints of hematuria and frequency, and is thought to possibly have a role as a cocarcinogen (22, 23). However, preoperative radiation has been shown to help reduce pelvic node recurrences following radical cystectomy.

The observation that heat may preferentially destroy malignant cells has been applied to CIS of the bladder. Hill et al (24) has had success with cystic lavage using isotonic saline warmed to 45°C. He reports promising results with minimal side effects.

An additional controversial conservative theraputic regime includes increasing the hydrostatic pressure in the bladder to a level between diastolic and systolic arterial pressure. Highly vascularized bladder tumors undergo hypoxic necrosis after a period of three to four hours in this procedure. This is accomplished by passing an inflatable balloon into the bladder lumen. Helmstein (13) has reported a 25% cure rate in CIS lesions. He has suggested that the central mechanism of tumor erradication in these cases involves the stimulation of an enhanced immune response to the necrosed tumor cells.

In summary, conservative treatment is most warranted in relatively asymptomatice patients with carcinoma-in-situ of the urinary bladder. Additionally, symptomatic patients with CIS deserve a trial period of less radical therapy before more aggesive steps are taken. However, in all cases close follow-up by urinary cytology, TURB with random biopsies every three months, and ongoing intravesical chemotherapy constitute required measures to catch early recurrences and to combat the development of invasive disease.

Open Surgical Approaches

Somewhat more radical approaches to bladder cancer include segmental resection. Partial cystectomy is recommended for patients who have advanced lesions which are inaccessible to TURB, are solitary, or reside within a diverticulum. However, since most carcinomas-in-situ are multifocal with indistinct borders this procedure has absolutely no value. Additionally, this procedure does not preclude the development of subsequent recurrences in the remaining bladder mucosa.

Radical treatment of carcinoma-in-situ of the bladder consists of some variation of total cystectomy, usually including urethrectomy, prostatectomy, distal ureterectomy, pelvic node dissection, and urinary diversion, most commonly through an ileal conduit.

The radical approach should be employed in patients who are reasonable surgical risks, for this is an extensive procedure, when the disease is multifocal and symptoms persist after a 6-month course of intravesical chemotherapy, when the disease involves the prostate or urethra, or when CIS continues to persist with multicentricity of space or time. Additionally, for a radical procedure to be considered for CIS, irritative symptoms should be persistent. CIS with severely irritative symptomatology has been associated with progression to invasion in 50%-80% of cases in one study (25). Finally, CIS associated with papillary carcinoma of the bladder has been shown to have a very high malignant potential, and as such should be treated aggressively (26).

Total cystectomy should include resection of the terminal 6-8 cm of the ureters with frozen section to ensure tumor free margins. A cutaneous ureteroileostomy provides drainage of urine. The major disadvantages of this procedure beyond care of the ileostomy include continual resorption of urea by the ileal conduit, renal stone formation, and stomal stenosis. Alternatively, urinary diversion may be achieved through a ureterosigmoidostomy. Complications of this variation include hyperchloremic acidosis and hypokalemia which require continual $NaHCO_3$ or NaCitrate administration as well as potassium supplements (27). Ureterosigmoidostomy is also often complicated by stenosis at the anastamotic site which may produce hydronephrosis, pyelonephritis and subsequent renal failure.

Total cystectomy carries a surgical mortality rate which has been reported to be as high as 7%−10% in 1979 (25) and sacrifices normal bladder and sexual functioning. It is easy to see why radical therapy is avoided whenever possible for the innocuous appearing CIS of the bladder.

Despite this long list of lethal and troublesome complications, cystectomy has the advantage of theoretically providing the only chance at a complete and total cure for CIS of the bladder. All urothelial tissue has been removed save for the proximal ureters. In addition, the recurrence rates for tumors reappearing in the ureters after cystectomy are vastly diminished (3% by Soloway, 198022). Indeed, the results of a Mayo Clinic Study by Utz et al (23) which were reported this year, found all 15 patients studied who underwent prompt cystectomy following the diagnosis of CIS of the bladder to still be alive with the longest follow-up covering a period of 69 months.

Future Trends in Prevention of Bladder Cancer

Efforts to combat carcinoma of the bladder in the future include attempts to better define the carcinogenic factors which most often lead to malignancy. In parallel with this are increasing efforts to educate and raise the level of awareness of the public to factors which are associated with the development of bladder tumors. An example of this is the influence of smoking as a carcinogenic force in the bladder as well as the lungs. In addition, screening programs for those at risk such as workers in certain industrial areas may be achieved when urinary cytology can become automated.

Another new area is that of chemoprevention. Compounds such as cis-retinoic acid, which is a vitamin A synthetic analog, is currently being evaluated for prophylactic potential. Large doses of pyridoxine which is thought to alter tryptophan metabolism has been linked with a reduction in the recurrence rate of superficial tumors of the bladder (15). Megavitamin C treatment is also receiving a great deal of attention.

Conclusion

Carcinoma-in-situ of the urinary bladder presents an unusual dilemma in the choice of management in that it demonstrates a heterogeneous array of behavior within a homogeneous histologic pattern. Since at this time the distinction between lesions which will quickly become invasive and require rapid aggressive intervention, and those which are more quiescent cannot be easily made, a compromise in strategy has been proposed.

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Letter to the Editor

HLA Antigens and Viral Antibody Titers in Identical Twins Discordant for Parkinson's Disease

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The etiology of Parkinson's disease is unknown. Studies on the possible role of a genetic factor (1–3), or an environmental agent, such as a virus (4–9), remain limited, contradictory and inconclusive. That an altered immune response to a viral agent linked to genetically determined histocompatibility alleles may be an underlying initiating event, has been actively considered (10). HLA antigens may influence receptor function for certain viruses and serve as a substrate for viral and chemical alterations of cells. Recently, we showed a significantly increased frequency of HLA-B14 antigen in association with classic postencephalitic Parkinsonism occurring in a particular ethnic group, but found no correlation between selected HLA antigen determinants and specific viral antibody responses (10).

An ongoing twin study of Parkinson's disease started at The Mount Sinai Medical Center in New York City in 1978, in an attempt to further clarify the relative importance of genetic and environmental factors, has shown zero concordance for the disease in the first 12 monozygotic twin pairs (11). Eleven pairs of these confirmed identical twins previously described clinically as discordant for Parkinson's disease (11), had studies on HLA-A, -B, and -C antigenic determinants by standard microlymphocytotoxicity techniques (by Dr. Pablo Rubenstein of the New York Blood Center) and serum viral antibody titers to herpes simplex virus type 1 (IHA), cytomegalovirus (IHA), measles (HI), rubella (HI), varicella-zoster (ELISA), and vaccinia (ELISA). By design, each twin pair had exactly the same HLA antigenic profile, with the unaffected cotwin serving as the "ideal" control for the parkinsonian proband.

Except for the antibody response to rubella virus, there were no significant differences between probands and unaffected cotwins in their response to the viral antigens tested. The geometric mean titer for rubella in the unaffected cotwin was 1.656 times higher than that in the proband [paired t (10 d.f.) = 2.39; $P < .05$]. There was no correlation between the presence or absence of a specific HLA antigenic determinant and viral antibody response. Since over 20 significance tests were done on these data, one must be cautious in interpreting the above statistically significant finding on rubella; for in any group of 20 significance tests, one can expect at least one test to be significant at the 0.05 level by chance alone (12). Thus, despite the efficiency and specificity of this cotwin control model study, the biological significance of the above results in these first eleven pairs of identical twins may only become clearer in the future when a comparably larger data base can be similarly analyzed.

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Variant Angina

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Abstract

It is now understood that Prinzmetal's variant form of angina pectoris differs from classical Heberden's angina in that ischemia results not from fixed obstruction of the coronary arteries but from coronary vasospasm. That this condition is most frequently found in conjunction with obstructive coronary artery disease, obscured for years its existence as a separate entity. Only recently, the use of ambulatory monitoring and provocation of spasm with ergonovine and the demonstrable relief elicited by nitroglycerine at angiography have made it possible to delineate clearly the degree to which spasm may contribute to anginal pain in the individual patient. Such delineation is critical in determining whether nitrites, beta blockers, calcium channel blockers or surgery will be the therapy of choice.

Theoretical models for the mechanism of vasospasm are appearing which are providing impetus for further research into the nature of the syndrome and pointing to more focused and appropriate therapeutic approaches.

Nearly 200 years ago, William Heberden provided us with the description of angina pectoris as we still know it today:

> There is a disorder of the breast marked with strong and peculiar symptoms, considerable for the kind of danger belonging to it, and not extremely rare, of which I do not recollect any mention among medical authors. The seat of it, and sense of strangling and anxiety with which it is attended, may make it not improperly be called angina pectoris.
>
> Those, who are afflicted with it, are seized while they are walking, and more particularly when they walk soon after eating, with a painful and most disagreeable sensation in the breast, which seems as if it would take their life away, if it were to increase or to continue . . . [I]n one or two very inveterate cases it has been brought on . . . by swallowing, coughing, going to stool, or speaking or by any disturbance of mind. . . . One has told me that it was aggravated by warm weather. (1)

The key feature in this definition is that effort, emotion or other provocation speeds up cardiac dynamics. The heart with coronary atherosclerosis cannot meet the demand for myocardial blood supply and hence, ischemia results.

There is another possibility, however, that cardiac activity does not become excessively stimulated, but rather that the coronary blood supply becomes acutely reduced below resting myocardial metabolic requirements. This has been attributed to spasm or functional narrowing of a coronary vessel. Heberden alluded to it:

> . . . [I]t be most probable, that a strong spasm be the true cause of this disorder . . . (1)

And the idea that spasm was the cause of anginal pain was suggested by both Latham (2) and Fothergill (3) in the 19th century.

In 1910 William Osler wrote:

> Let us now consider in what condition we actually see spasm of the arteries and by spasm I mean a persistent contraction leading to ischemia, with disturbance of function of the parts supplied,
>
> The spasm is not always painful, but it may be associated with intense pain.
>
> Spasm or narrowing of a coronary artery, or even of one branch may so modify the action of a section of the heart that it works with disturbed tension, and there are stretching and strain sufficient to arouse painful sensations. . . . I do not know of any better explanation of anginal pain. (4)

The landmark description of spastic or variant angina was made by Myron Prinzmetal in 1959 (5). His description emphasized pain occurring at rest and often at night and usually not related to effort. It tends to occur in cycles of paroxysms that may last for weeks at a time. This condition may present as an intermediate ischemic syndrome or unstable angina or impending infarction.

The electrocardiogram (ECG) of classical Heberden's angina shows ST segment depression.

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But Prinzmetal noted profound ST segment shifts upward during attacks of variant angina with a return toward normal following pain (Fig. 1). These ECG patterns are readily explained electrophysiologically as due to differences in the degree of myocardial ischemia. ST segment depression occurs with subendocardial ischemia, while ST elevation means that the process also extends up into the subepicardial layer (transmural ischemia), representing a more severe degree of myocardial ischemia (6). While Prinzmetal described ST segment elevation as a hallmark of variant angina, ST segmental depression can occur with any anginal attack, whether classical or variant. According to an extensive monitoring study by Maseri, one of the pioneer workers in clarifying the pathophysiology of this entity, ST segment elevation occurred in 60% of all anginal episodes while ST segment depression was seen in the remaining 40%. Alternating ST-T changes were seen in about 15% of the patients and ST segment elevation occurred without pain 37% of the time (7). ECG monitoring showed that only about one-third of all ECG episodes had associated pain. This was first noted by Osler in 1910. It becomes apparent, then, that even catastrophic myocardial events might occur without any ischemic symptoms. In about 60% of patients, pain occurred only at rest while the pain occurred both at rest and with exercise in the remaining 40% (8). Fuller et al and Yasue et al have shown that exercise induced angina in some instances is related to myocardial ischemia caused by spasm, not by fixed coronary obstruction (9, 10). Thus, painless ischemia and ST segment depression as well as elevation can all be components of the vasospastic or variant anginal syndrome. Maseri has estimated that at least 10% of all anginal attacks are vasospastic in origin. So this entity can no longer be considered a rarity. Maseri's work also revealed that arrhythmias occurred in 20% of attacks and that myocardial infarction eventuated in about 20% of the cases (10).

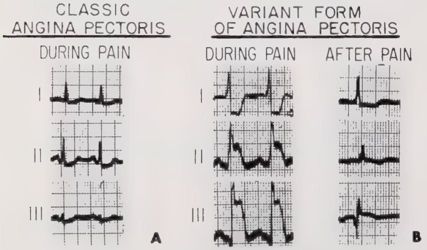

FIG. 1. Comparison of electrocardiographic characteristics of classic angina pectoris and the variant form. A. Classic angina pectoris: ST segments show depression without reciprocal ST elevation. Electrocardiogram obtained after exercise. B. Variant form of angina pectoris: During spontaneous pain, ST segments show elevation in leads II and III with reciprocal ST depression in lead I. Immediately after pain, the electrocardiogram returns to normal or to prepain pattern. (Reproduced with permission from Prinzmetal, M., Kennamer, R., Merliss, R., Wada, T. and Bor, N.: Angina Pectoris. I. A Variant form of Angina Pectoris: Preliminary Report. American Journal of Medicine 26:375, 1959.)

The development of coronary arteriography has taught us much about the anatomic aspects of this syndrome. In spasm, acute coronary occlusion may take place; the occlusion may be complete or incomplete and either segmental or diffuse. Even more important, this may occur with or without concomitant atherosclerosis. It must be appreciated that the two processes are far from mutually exclusive. In fact, the most common occurrence of vasospasm is in association with established coronary atherosclerosis. Finally, spasm occurs not only in the coronary arteries but at the arteriolar level as well. Thus, small vessel constriction may be present as well as large vessel spasm (11).

Since vasospasm can be indistinguishable from coronary atherosclerosis on arteriography, it is necessary to determine the etiology of any stenosis observed. The administration of nitroglycerine is of value in this respect. Yet even when administration of nitroglycerine completely relaxes an artery which previously exhibited a severe stenosis, it may not be known whether the spasm has resulted, as is quite common, from mechanical irritation of the vessel wall or whether one has encountered a true spontaneous spasm of the vessel (Fig. 2). When observed stenosis has been produced by spasm alone, administration of nitroglycerine will usually relax the vessel, demonstrating the normal coronary artery which had been in spasm (Fig. 3).

More commonly, however, one identifies coronary vasospasm in association with coronary atherosclerosis. In such cases, the vasospasm intensifies the ischemic process produced by the fixed obstruction. In these circumstances the administration of nitroglycerine will dilate the spasm and unmask any fixed obstruction (Fig. 4).

Occasionally spasm can occur at the arteriolar level without large vessel involvement and may lead to precisely the same clinical ischemic picture (11).

Functional Aspects

Segmental perfusion deficits during attacks of spastic angina are often quite severe and tend to

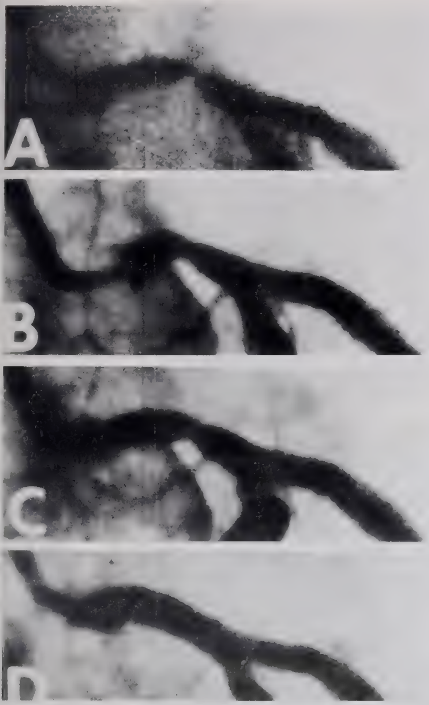

FIG. 2. Catheter in the mouth of the left coronary artery. A. Note adjacent severe stenosis. B, C. With the administration of nitroglycerine the artery begins to relax and D, relaxes completely.

be transmural in nature and can be recorded by Thallium-201 perfusion scanning (Fig. 5).

Coronary sinus blood flow has been recorded during ergonovine-induced coronary spasm utilizing the thermodilution technique. During the period of pain, changes in the ST segment of the ECG were noted along with decrease in coronary sinus flow. Most important is the primary reduction in coronary blood flow. Blood pressure was lower during the attack than afterward and coronary sinus oxygen content dropped as the arteriovenous oxygen difference widened during spasm and returned after the attack to almost a hyperemic value (Fig. 6) (12). Such evidence points to a primary spasm of a coronary artery; a functional obstruction with a drastic reduction in segmental coronary blood flow along with changes in myocardial metabolism resulting in production of lactate by myocardium.

Figure 7 shows an ECG of a patient with the typical ST segment elevation of profound transmural ischemia so marked as to suggest that an infarct was about to occur (13). ST changes then receded, all within 15 minutes. The patient had a steady heart rate throughout. Note also the elevated blood pressure. Contrary to what is often seen in classical angina, this patient remained persistently hypertensive before, during, and after the attack. To recapitulate, then, one looks for hemodynamic change at the time of an attack of typical angina, but the absence of change or even the presence of abnormal hemodynamics may bear no direct relationship to the cause of the anginal episode, that is, spasm or fixed obstruction.

The functional consequences may be hemodynamic. There may be segmental asynergy in the zone of reduced coronary flow, overall poor contraction of the ventricle, reduced cardiac output and elevated left ventricular enddiastolic pressure. The blood pressure and heart rate are usually not altered over control, whatever that control may have been.

Figure 8 shows a right coronary artery in spasm. The vessel was nearly obliterated but then restored to normal calibre with nitroglycerine. A ventriculogram during the ischemic episode revealed an inferoposterior segment of asynergy looking exactly like a postmyocardial infarction scar (14). Furthermore, the mechanical consequences may be devastating and simulate what is seen during acute myocardial infarction except that the changes usually are reversible (Fig. 9) (15).

Severi followed a group of 138 patients who had variant angina for periods of two to eight years. Ninety-eight of 107 patients who underwent angiography had associated coronary artery disease and nine of these had normal coronary arteries. During the month following initial hospital admission 28 patients (20%) had an acute myocardial infarction and five patients, or about three percent died. Of the 133 survivors, 120 were treated medically: seven of them died and four suffered an acute myocardial infarction. While no patient with only single vessel disease died, one patient with normal coronary arteries died suddenly during the third follow-up year. During hospitalization his electrocardiogram had shown several episodes of ST segment elevation followed by ventricular tachycardia or ventricular fibrillation during the resolution phase. On arteriography this patient was shown to have right coronary artery spasm with complete occlusion. This is not an isolated finding and suggests that this disorder may be the substrate of sudden cardiac death in the absence of "organic" heart disease (16).

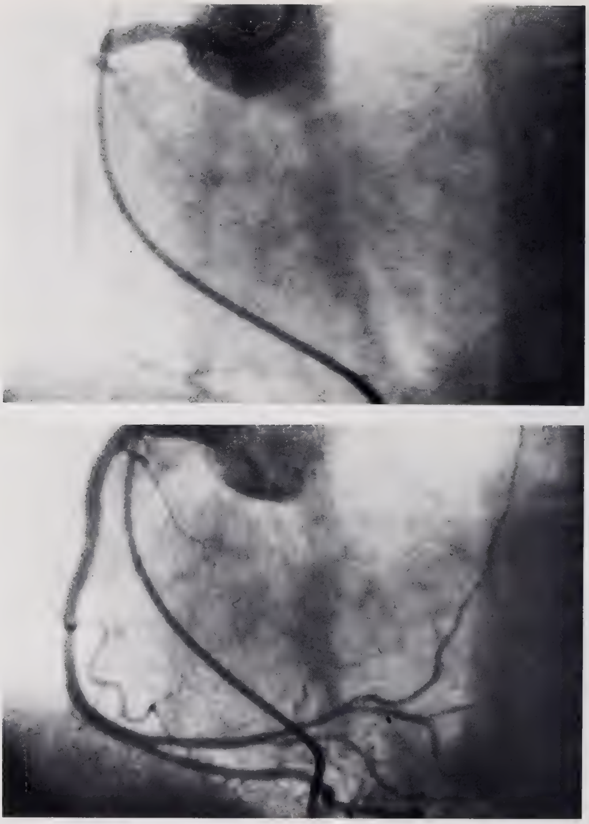

FIG. 3. Right coronary artery with catheter in place. A. The vessel beyond it is of normal calibre, then it narrows in spindly, diffuse fashion. One cannot be confident whether this is a functional spasm or diffuse coronary atherosclerosis. B. Following nitroglycerine, however, the vessel fills out completely, demonstrating a normal coronary artery which had been in severe spasm.

Cobb and his associates in Seattle reported that patients who sustain but recover from primary ventricular fibrillation, have no myocardial infarction and are shown at angiography to have normal coronary arteries, are prone to recurrence of arrhythmia which is often fatal (17). They are also more likely to die ultimately of an electrical or "sudden" death than those with coronary disease and an acute myocardial infarction. They may well be persons who have coronary vasospasm without angina.

That there were no acute myocardial infarctions in Severi's normal coronary artery group may have been a statistical vagary of his series because these same workers have reported occurrence of subsequent acute myocardial infarction in patients with ostensibly normal coronary arteries. Maseri argues persuasively that some of the infarcts occurring in patients who have normal coronary arteries take place against a vasospastic background, perhaps as an initiating event to local thrombosis (18).

Theories of Vasospasm

The mechanism of coronary vasospasm is not yet fully understood. The assumption is that

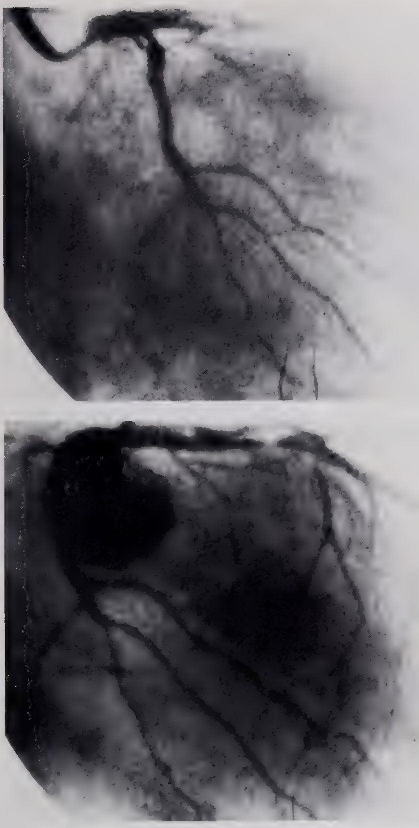

FIG. 4. Left coronary artery. A. There is slight narrowing of the circumflex branch with normal distribution of the marginal branches. Beyond the midportion of the anterior descending and a diagonal there is no vasculature seen. This may represent total occlusion of this vessel with no antegrade blood supply, or that the latter is coming from another source. B. When nitroglycerine is given, the blood vessels of the circumflex system become much larger and one visualizes the distal anterior descending circulation. There is a major septal perforator, but proximally there is also a fixed coronary arterial obstruction.

events must take place which influence the contractile capacity of these muscular arteries such that they contract. Various mechanisms may play a role in this syndrome. Vessels can constrict or dilate through activity of the adrenergic nervous system. There are both alpha and beta receptors on the smooth muscle cells. When there is sympathetic nervous system stimulation, norepinephrine can affect either an alpha or beta adrenergic receptor. Alpha stimulation leads to muscular constriction while beta stimulation leads to dilatation. Some theorists suggest that there may be an excess of alpha receptors or a deficiency of beta receptors (in number or affinity) (19), either one leading to constriction of the arterial smooth muscle and spasm. These receptors may also be stimulated through the cholinergic system (20). It is possible that central nervous system stimuli may affect vascular smooth muscle through autonomic nervous system pathways.

A most attractive hypothesis is that there is something defective in the prostaglandin metabolism. Prostaglandins are ubiquitous fatty acids generated from arachidonic acid. Depending on

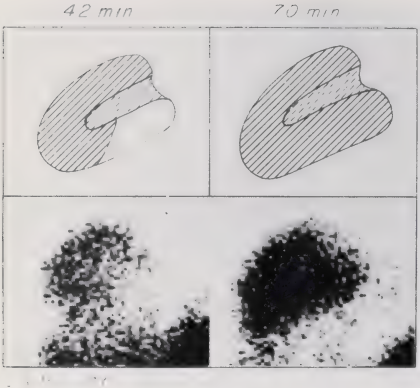

FIG. 5. Tl-201 scan showing transmural segmental perfusion deficit during variant angina with return to normal following nitroglycerine.

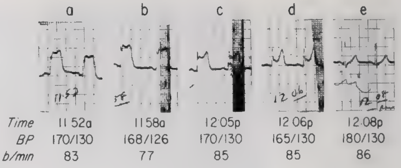
a
b
c
d
e
Time 11 52a 11 58a 12 05p 12 06p 12 08p
BP 170/130 168/126 170/130 165/130 180/130
HR b/min 83 77 85 85 86

FIG. 7. Serial recordings of lead V_4 during and after an episode of variant angina on day 1 of hospitalization. Blood pressure and heart rate before episode of pain were 175/130 and 85 beats/min respectively. (Reproduced from Madias, J. E.: The syndrome of variant angina culminating in acute myocardial infarction. Circulation 59:301, 1979 by permission of the American Heart Association, Inc.)

the tissue, different prostaglandins are synthesized with different biological properties. For example, in the endothelium, when arachidonic acid is converted into a prostaglandin, prostacyclin is formed. This is a dilator of smooth muscle and also a deaggregator of platelets. So endothelial prostaglandin synthesis leads to a compound which causes smooth muscle dilation. Prostacyclin synthesis decreases as one moves outward in the arterial wall layers (Fig. 10).

Platelets also have a prostaglandin pathway but here the compound synthesized in greatest amounts is thromboxane A_2. This particular prostaglandin has two features exactly opposite those of prostacyclin: the first is to make platelets stick to each other and to the endothelium, and the second is to cause powerful constriction of the medial smooth muscle when thromboxane migrates through the intima.

The prostaglandin hypothesis holds that there is something wrong with platelets or with endothelium in the relative synthesis of thromboxane or prostacyclin, and through this mechanism an excessive constriction of medial smooth

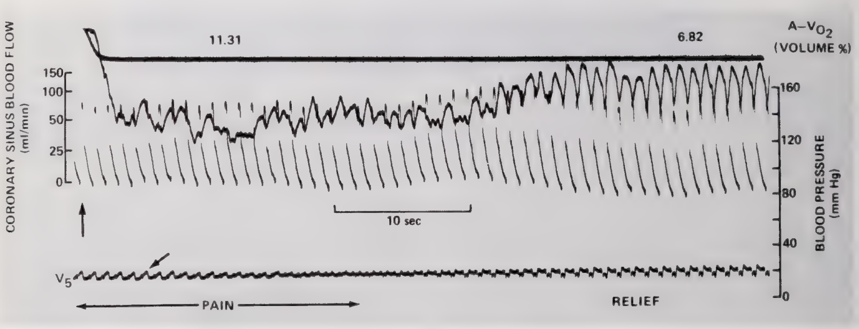

FIG. 6. Continuous recording of thermodilution coronary sinus blood flow, blood pressure and V_5 electrocardiogram during relief from spontaneous chest pain. The coronary sinus injection was begun (vertical arrow) immediately after collecting coronary sinus sample for determination of oxygen content at the peak of chest pain, accompanied by ST segment elevation (slanted arrow). Flow reached a nadir of 46 ml/min, and gradually rose to 135 ml/min as the pain eased the ST segment returned to the control state. The blood pressure remains constant at 145/80 mmHg. The coronary sinus arteriovenous oxygen difference (A-VO_2) narrows as pain is relieved. A baseline measurement of coronary sinus flow recorded moments before the onset of pain was 96 ml/min, and coronary sinus A-VO_2 was 9.8 volume percent. (Reproduced from Ricci, DR., Orlick, A. E., Doherty, P. W., Cipriano, P. R. and Harrison, D. D.: Reduction of coronary blood flow during coronary artery spasm occurring spontaneously and after provocation by ergonovine maleate. Circulation 57:393, 1978 by permission of the American Heart Association, Inc.)

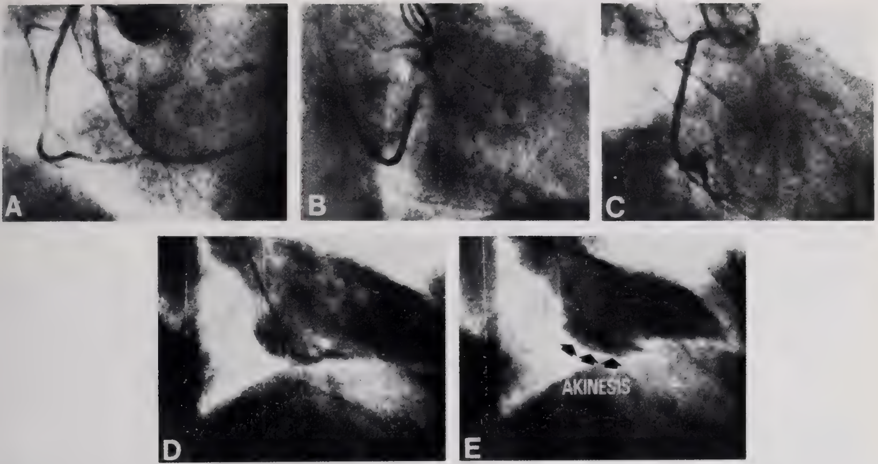

FIG. 8. Right coronary arteriograms in left (A) and right (B and C) oblique projections, and left ventriculogram, right anterior oblique projection (D and E). A. The right coronary artery has a normal outline. A catheter in the center of the field is situated in the coronary sinus. B. Injection after the onset of chest pain reveals complete obstruction of the main trunk (arrow) of the right coronary artery. The coronary sinus catheter is now located toward the lower left of the field. C. A repeat right coronary arteriogram after recovery from ventricular fibrillation shows a normal right coronary outline. D. Left ventriculographic frames during diastole (D) and systole (E) reveal akinesia of the inferior left ventricular wall (arrows), consistent with old inferior myocardial infarction. (Reproduced with permission from Wiener, L., Kasparian, H., Duca, P. R., Walinsky, P., Gottlieb, R. S., Hanckel, F. and Brest, A. N.: Spectrum of coronary arterial spasm. Clinical angiographic and myocardial metabolic experience in 29 cases. Am J Card 38:953, 1976.)

muscle can occur. It has also been suggested that atheromatous areas of the artery may be deficient in synthesizing prostacyclin. Furthermore, platelets may adhere to diseased intimal surfaces and generate thromboxane locally. The clinical facts to support or deny that these biochemical mechanisms cause spasm are sparse or simply lacking. The question has been addressed whether aspirin, which inhibits synthesis of prostaglandins from arachidonic acid, can inhibit spasm. Robertson et al and Chierchia et al were unable to block spasm and variant angina when aspirin blocked platelet thromboxane production (21, 22).

A final hypothesis holds that the smooth muscle itself is abnormal and responds excessively to any constrictor stimulus, for example, the ergotamine response (Fig. 11) or to calcium excess (23).

Sabom and coworkers studied a group of patients who had variant angina and were able to document angiographically both a spontaneous attack and one induced using ergonovine as the agonist. The upper left panel of Figure 12 is an angiogram during spontaneous pain with obliteration of the left anterior descending system. Nitroglycerine caused reconstitution of this blood vessel through vasodilation. The patient was then given ergonovine which again induced severe spasm of the left anterior descending artery. Nitroglycerine once again returned to artery the normal calibre (24).

Heupler performed a study to determine whether the ergonovine response was specific in diagnosing vasospastic angina (25). A positive response to ergonovine is believed virtually tantamount to having variant angina. Maseri believes that this suggests there is something fundamentally wrong with the coronary smooth muscle in that it goes into spasm so readily.

Certain clinical situations arouse suspicion that angina may have a vasospastic component. This is certainly the case when the patient exhibits pain at rest or if pain *follows* exercise rather than occurring during exercise. Pain provocation which is unpredictable may be an important clue. The variant angina patient is frequently the very patient in whom one might be inclined to doubt the presence of any cardiac disease whatever. Patients with unstable or intermediate anginal syndromes may have spasm. Finally, unexplained

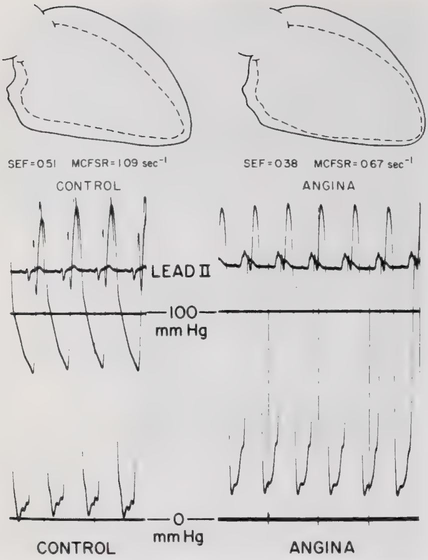
SEF=0.51 MCFSR=1.09 sec^{-1}
CONTROL
SEF=0.38 MCFSR=0.67 sec^{-1}
ANGINA
LEAD II
100
mm Hg
0
mm Hg
CONTROL
ANGINA

FIG. 9. Top. Left ventricular contraction plots before and during angina. The solid line represents the left ventricular enddiastolic perimeter and the broken line represents endsystole. During angina there was a reduction in the systolic ejection fraction (SEF) and in the mean circumferential fiber shortening rate (MCFSR), inferoapical hypokinesis developed. Bottom. Left ventricular pressure and lead II of the electrocardiogram recorded during angina. There was little change in heart rate or in left ventricular systolic pressure during pain. The enddiastolic pressure increased from 7 to 34 mmHg. (Reprinted with permission from Gaasch, W. H., Adyanthaya, A. V., Wang, V. H., Pickering, E., Quinones, M. A. and Alexander, J. K.: Prinzmetal's variant angina: Hemodynamic and angiographic observations during pain. Am J Card 36:684, 1975.)

syncope brought on through the frequent and severe associated arrhythmic or conduction disturbances may be the only manifestation of a variant anginal attack.

To elucidate clinical suspicion, an ECG taken at the time of an attack can be extremely helpful. Twenty-four hour Holter monitoring is probably the most important clinical tool available. A patient may go for weeks or months without symptoms, with pain appearing suddenly in salvoes. This is the time for a Holter monitor, if possible for a number of days in a row, to try to "capture" the ST-T changes. One must bear in mind, of course, that ST depression may occur as frequently as ST elevation, although usually without tachycardia on the ECG.

Laboratory detection involves performance of coronary angiography during acute episodes to document spasm which may be either spontaneous or induced by agonists such as ergonovine. If the laboratory is equipped to measure coronary sinus blood flow, recording a sudden decrease during coronary spasm and recovery afterward is a very clear and simple way to obtain additional primary diagnostic information with little or no risk to the patient (Fig. 6).

Therapy

The objective of therapy is to relax constricted coronary smooth muscle. This can be done directly or indirectly. The most effective direct smooth muscle dilators are the nitrites and the calcium channel blockers such as verapamil, nifedipine and diltiazem. There is some evidence that smooth muscle can be relaxed by indirect means. The Stanford group has examined the alpha blockers, phentolamine and phenoxybenzamine, and shown that in patients with alpha blockade and vasodilatation can be achieved (26).

Beta blockers are controversial. Some workers indicate they should never be used in variant angina as they might precipitate an attack. They rarely cause any serious problems for the average patient, however. From another perspective, when a patient has what appear to be anginal attacks and the response to beta blockers is poor despite achievement of pharmacologic blockade, then perhaps the angina is not atherosclerotic but rather vasospastic in origin. Contrariwise, Guazzi has stated that very large doses of beta blockers actually can be helpful in variant angina (27).

The therapy *not* offered is as important as the therapy prescribed. It is not unheard of that saphenous vein bypass grafts have been performed only to discover at postoperative evaluation that a bypassed artery was perfectly normal and that vasospasm had been mistaken for an anatomic occlusion (Fig. 12). Such mistakes are not uncommon and can be made unless an active search is made for vasospasm as a cause for any obstruction seen on angiography. When there is doubt, one should take cines before and after administration of nitroglycerine. Revascularization surgery is not the answer unless the patient has coronary obstruction significant enough in and of itself to require bypass (28–30).

Nitrites have been shown to be extremely effective agents in the management of variant angina as has already been stated (Figs. 13, 14) (31).

Calcium slow channel antagonists that block

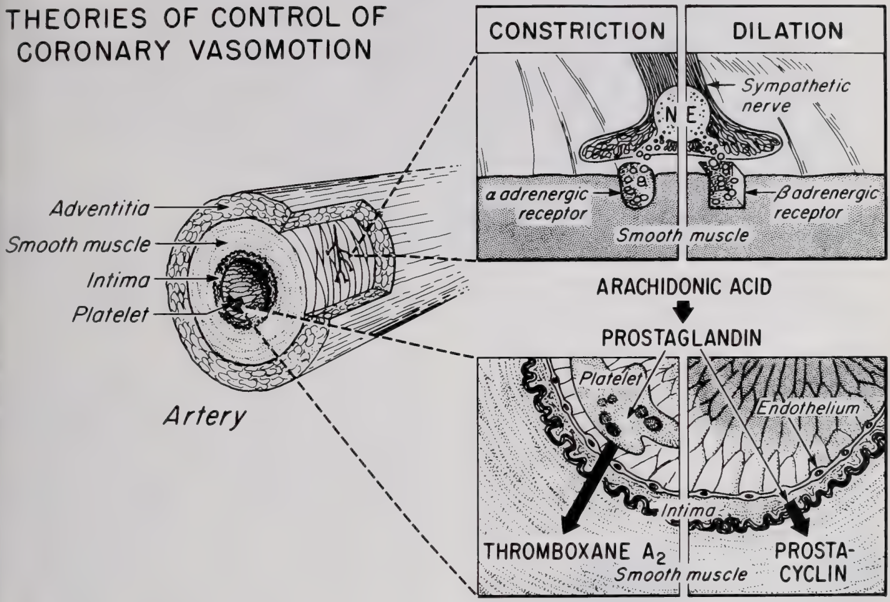
THEORIES OF CONTROL OF CORONARY VASOMOTION
CONSTRICTION
DILATION
Sympathetic nerve
N E
α adrenergic receptor
β adrenergic receptor
α
β
Smooth muscle
Adventitia
Smooth muscle
Intima
Platelet
Artery
ARACHIDONIC ACID
PROSTAGLANDIN
Platelet
Endothelium
Intima
THROMBOXANE A2
PROSTA-CYCLIN
Smooth muscle

FIG. 10. The muscular coronary artery is shown in cross section. Vascular smooth muscle is under control of the sympathetic nervous system (as depicted) and the cholinergic system as well. Prostaglandin also may affect smooth muscle. Prostacyclin derived from vascular intima effects dilatation while thromboxane A_2 generated by activated platelets causes constriction (see text).

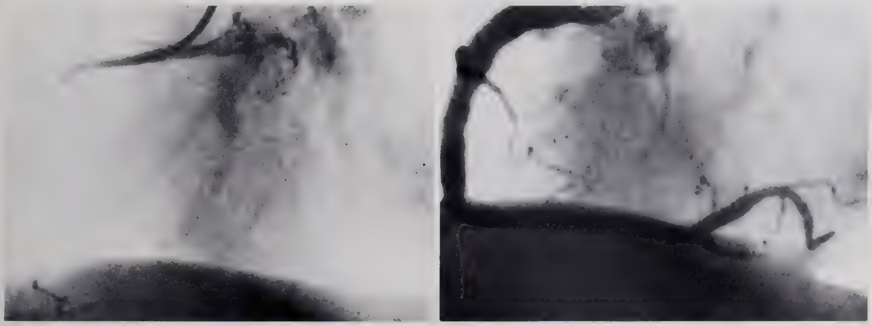

FIG. 11. A. Right coronary artery in a patient who had severe unstable angina pectoris suspected of being variant angina. Following administration of ergonovine the large coronary artery constricts to a size approximating the diameter of the catheter and the distal vessel is practically obliterated. The patient had chest pain and was given nitroglycerine intravenously. B. Both spasm and pain disappeared and the diagnosis was confirmed.

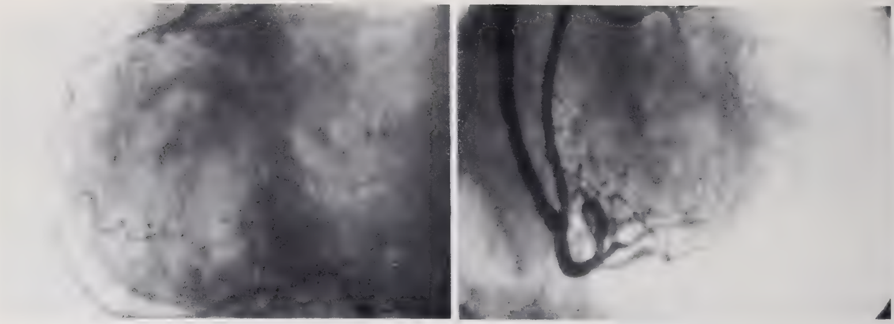

FIG. 12. Saphenous vein bypass graft was performed on this normal right coronary artery after angiography demonstrated what appeared to be a fixed occlusion but was, in fact, vasospastic. Nitroglycerine would have relaxed the vessel and delineated the true nature of the obstruction.

the calcium inward current are effective in variant angina because they relax coronary smooth muscle. Using a study design like the one elected for the nitrite study, Parodi et al demonstrated a significant decrease in the numbers of attacks of angina with verapamil (Fig. 15) (32).

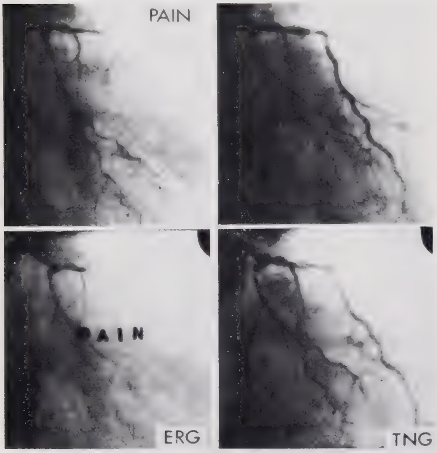

FIG. 13. Right coronary artery. Upper left: Angiogram obtained during an episode of spontaneous pain with ST elevation. Upper right: Angiogram after pain subsided. Lower left: Pain provoked by ergonovine. Lower right: Following nitroglycerin. ERG = ergonovine. TNG = nitroglycerin. (Reproduced from Curry, R. C. Jr., Pepine, C. J., Sabom, M. B., Feldman, R. L., Christie, L. G. and Conti, C. R.: Effects of ergonovine in patients with and without coronary artery disease. Circulation 56: 807, 1977 by permission of the American Heart Association, Inc.)

Nifedipine is another calcium channel blocker which is now available in this country. It has been demonstrated to reduce not only the frequency of attacks but also the number of nitroglycerine tablets used (Fig. 16) (33–36).

These agents will play a major role in the management of this important disease and it may be that this class of drugs will be additive to the nitrites and the beta blockers. Yet there are certain theoretical concerns about giving calcium antagonists along with beta blockers since they are negatively inotropic. Although they decrease contractility to some degree, Ferlinz has shown

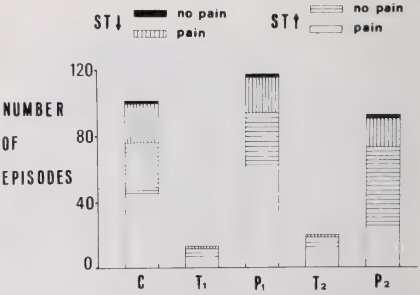

FIG. 14. Pooled results in 12 patients. The reduction in the number of the ischemic episodes during treatment with isosorbide dinitrate (T_1 and T_2 is similar both for episodes with S-T elevation (S-T) and with S-T depression (S-T), either with or without pain. (Reprinted with permission from Distante, A., Maseri, A., Severi, S., Biagini, A., and Chierchia, S.: Management of vasospastic angina at rest with continuous infusion of isosorbide dinitrate. A double crossover study in a coronary care unit. Am J Card 44:536, 1979.)

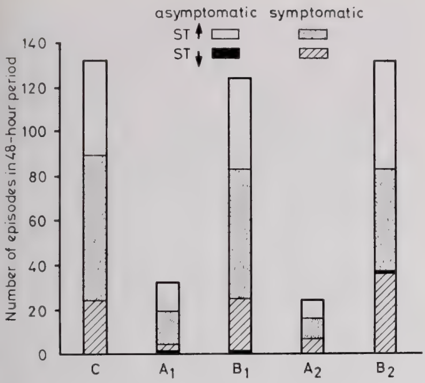

FIG. 15. The total number of episodes in 12 patients in each 48-hour period of the trial. C indicates run-in period; A_1, A_2 verapamil periods; B_1, B_2 placebo periods. Control and placebo periods show similar number and type of ischemic episodes, while during treatment with verapamil there is a conspicuous reduction in frequency of all types of episodes. (Reproduced with permission from Parodi, O., Maseri, A., and Simonetti, I.: Management of unstable angina at rest by verapamil. A double-blind cross-over study in coronary care unit. Brit Heart J 41:171, 1979.)

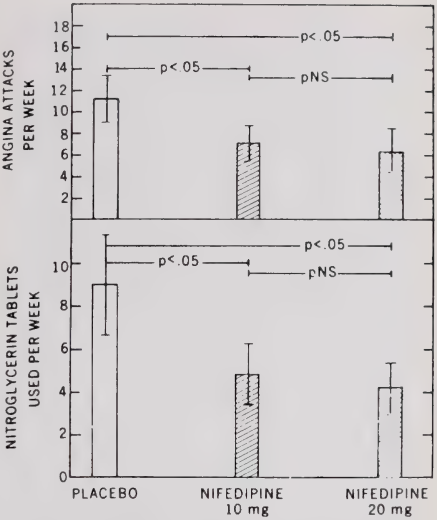

FIG. 17. Effect of nifedipine therapy (10 mg and 20 mg orally every 8 hours) compared with that of placebo on frequency of anginal attacks and nitroglycerin used per week. Values are mean ± standard error of the mean. NS = not significnt; p = probability. (Reproduced with permission from Moskowitz, R. M., Piccini, P. A., Nacarelli, G. V. and Zelis, R.: Nifedipine therapy for stable angina pectoris: Preliminary results of effects on angina frequency and treadmill exercise response. Am J Card 44:813, 1979.)

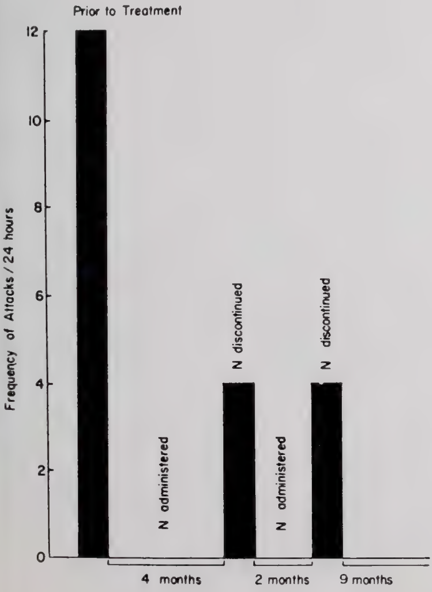

FIG. 16. Clinical course of patient. Each episode of nifedipine (N) withdrawal resulted in recurrence of ischemic symptoms. Reinstitution of nifedipine therapy promptly prevented anginal episodes. (Reproduced with permission from Goldberg, S., Reichek, N., Wilson, J., Hirshfeld, J. W. Jr., Muller, J. and Kastor, J. A.: Nifedipine in the treatment of Prinzmetal's (variant) angina. Am J Card 44:809, 1979.)

that they also dilate the peripheral arterioles and "unload" the heart in a most favorable manner (37). Thus, negative myocardial effects are counteracted by a reduction in impedance. Theoretically, then, although both beta blockers and the calcium channel inhibitors depress myocardium, in actual practice this is not frequently an important consideration. Obviously, if the patient has clinical cardiac failure, one probably would not use either class of drug. But in the management of classical Heberden's angina, the nitrites and beta blockers are appropriate while if variant angina is suspected then nitrites or calcium inhibitors, or both, are correct. In some cases all three drugs may be required.

Spasm may play an important role in virtually every aspect of the natural history of coronary artery disease whether in the anginal syndromes, the unstable intermediate syndromes or perhaps in the pathogenesis or in the course of acute myocardial infarction (18). The syndrome often requires high clinical awareness from the first history taking to careful ECG observation for us to recognize the possibility of the diagnosis, then careful ambulatory ECG monitoring and coronary angiographic demonstration of spasm are required to make the diagnosis. Only careful and complete diagnosis will permit application of the appropriate, effective therapy.

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A Consideration of the Cholinergic Nerve Supply to the Pancreas

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This subject is difficult and becoming more so. Part of the difficulty is the price we pay for the convenience of computerized literature searches. Wholesale reliance on these, which bibliographies indicate is now distressingly common, has drawn a blind across work more than ten-years old. Advancement depends on the past; if the past is curtailed so must our advance be. Total reliance on limited computer literature searches is having this effect at the moment, in my view.

Fifteen years ago, the following picture which I propose to examine in the light of some old and some new literature might have been drawn up:

1. The pancreas is controlled by secretin and CCK and directly by the vagi and by cholinomimetics.
2. The vagi in addition to their direct stimulating action render the gland more responsive to the two hormones.
3. The release of the duodenal hormones is facilitated by the vagi.
4. Both hormones require, for release, local anesthetic sensitive receptors in the mucosa. CCK but not secretin release requires a local cholinergic mechanism which is atropine and ganglionic blocker sensitive.

1. Proof of the existence and physiologic importance of secretin and CCK is no longer questioned and moreover it is not part of the purpose of the discussion.

Vagal stimulation has been known for many years to increase enzyme secretion [18, 52]. Even in the species in which it was once thought to have no effect, the effect of vagal stimulation of fluid and enzymes especially, became obvious once constriction of the duct, first recognized by Anrep [2] as the mechanism for Popielski's [55] vagal inhibition, had been eliminated. In some species such as pigs [23, 25, 42], cats [35] and rats [37], the positive effect of vagal stimulation on pancreatic fluid and enzyme secretion is consistent and obvious. Many [7] have found that acetylcholine stimulates enzyme secretion in isolated pancreatic tissue. Hokin et al [24] have verified this in isolated slices of pigeon pancreas. The gastropancreatic secretory reflex [77] which stimulates both protein and fluid secretion is dependent on the vagi. Harper et al [16] have demonstrated a vagovagal stimulatory effect in anesthetized cats. Hickson [23] and Magee et al [42] have shown that vagal stimulation is a potent augmenter of pancreatic fluid secretion in pigs. Bourde et al [5] have shown the same in conscious dogs while Kaminski et al [28], also in conscious dogs, have produced increases in volume, bicarbonate, and protein secretion on vagal stimulation. Thus, there is no doubt that the pancreas, fluid and enzyme secretion, does respond to cholinergic stimulation even under circumstances when it is clearly the sole stimulus. The evidence, therefore, still favours proposition 1.

2. Do the vagi render the gland more sensitive to hormones?

Secretin

Magee et al [42] have shown a more than additive increase in water secretion in pigs with vagal stimulation and secretin together. Brown et al [6] have shown this in anesthetized cats; so did Harper et al [16] in the course of their experiments on vagovagal reflexes in cats and Henriksen et al [22] and Guzman et al [14] on anesthetized dogs. Few experiments of this type have been carried out. Many [13, 50, 69, 74] have noticed in intact animals and *in vitro* that even if cholinergic agents themselves had little effect on fluid volume they definitely augmented the response to secretin. This has been found in the rat (Lin et al [37], Pap et al [51], the rabbit (Solberz et

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al [66]), the cat (Lenninger et al [35]), the dog (Nakamura et al [50], Thomas [70]), the pig (Holst [25], Magee et al [42]) and *in vitro* (Vaysse et al [74]).

If cholinomimetics and vagal stimulation accentuate the pancreatic response to secretin because they exert a tonic facilitation, as has been concluded by many from the above experiments, then the converse, a decrease in the efficacy of secretin, ought to follow interruption of vagal impulses to the gland whether by vagotomy, atropine or ganglionic blockade. This seemingly simple experiment has often been tried and the results, curiously, have been inconclusive.

The literature on the subject has reports of increase, decrease or no change in the responsiveness of the gland to secretin following atropine or vagotomy.

Magee et al [40] and Lenninger et al [34] concluded that the pancreas was not as sensitive to secretin and that the daily secretion of fluid and enzymes was diminished after bilateral vagotomy in conscious dogs. Atropine and ganglionic blockade depressed the responsiveness to both secretin and CCK in pigs [27]. In the earlier experiments in dogs, the slopes of the secretin dose response lines with atropine and after vagotomy were different but the V_{max} was unchanged. It was concluded that the vagi acted on the pancreas, to increase end organ sensitivity, much as they are said to do on the gastric fundus. Singleton [64] found secretin ineffective in man after vagotomy and Pfeffer et al [53] found a 50% decrease in response. Wormsley [78] has found the same for bicarbonate and to a lesser extent for the protein responses to secretin and CCK.

What are the arguments against these ideas? Tankel and Hollander [67] found the pancreas in two of four dogs more sensitive to Lilly secretin after vagotomy than before. Routley et al [59] found the same using thirty conscious dogs with secretin from an unspecified source. Denervation sensitivity was postulated as the cause. It is tempting to dismiss this as a case of small numbers and impure hormone, as Magee et al [40] found the same with Boots secretin, which they showed to be contaminated with CCK, but not with the Vitrum preparation which did not increase enzyme secretion. A few others have noticed augmentation of the bicarbonate and fluid response by very large doses of atropine or atropine with Boots secretin plus CCK or by atropine after intraduodenal peptone [20, 48, 61, 71, 76]. Debas et al [8] claimed that extragastric and truncal vagotomy reduced only basal secretion and the response to feeding but had no effect on exogenous secretin, actually his data showed, with doses of secretin up to 1 unit/kg/hr, a significantly reduced bicarbonate response. Moreland and Johnson [49] found that, after vagotomy, fluid and bicarbonate stimulation was augmented by low doses of secretin, with moderate to high doses there was no difference. Only three animals were used in these experiments. To get the degree of significance claimed, n must have been experiments rather than animals, thus these experiments must be reckoned as inconclusive. Bayliss and Starling [4], Mellanby [45], Babkin [3], Agren [1] and Harper and Raper [17] found that atropine did not affect the pancreatic response to secretin in experiments on anesthetized animals. Thomas and Crider [71] and Levin [36] as quoted in Gregory (Fig. 83 p. 179), using conscious dogs, have found that atropine diminished the secretin response. Henriksen [20], using Boots secretin by bolus injection, found, as had Magee et al [40], that vagotomy or vagal block did not depress its effect. Singer et al [62] have found that in the intact pancreas atropine depressed secretin stimulated bicarbonate, and thus presumably fluid, and also protein. Atropine affected neither bicarbonate nor protein from the transplanted pancreas. This is in accord with Magee et al [40] who found no atropine effect after vagotomy. Thambugala and Baron [68] in dogs and Wormsley [78] in man found that truncal vagotomy reduced the response to secretin. In the dog experiments, this was temporary as the animals became hypersensitive after six months. Their explanation for this was a functional take over by the splanchnics which White et al [77] saw after vagotomy during their study of the gastropancreatic reflex.

Virtually all who have looked for it have found that the protein of secretin stimulated juice, which is usually low and constant in amount, is depressed by atropinization, by vagotomy, and by ganglionic blockade.

We conclude, therefore, that the evidence supports the idea that vagal stimulation and cholinomimetics do increase the responsiveness of the gland to secretin. The converse using vagotomy and blocking agents is not as clear; the balance is in favor of decreased sensitivity of the intact gland following blockade. The evidence against (cited above) can often be explained by anesthetized animals, impure secretin, massive doses of secretin or atropine or improper statistics.

CCK

Modern evidence derived from *in vitro* studies has made it likely that the action of vagi and cholinomimetics resembles the action of CCK on the acini since both are accompanied by a release of calcium and seem, unlike secretin, not to involve cyclic AMP [44]. However, the evidence *in vivo* for a common mechanism of action is much less clear. Synergism is evident between secretin and the cholinomimetics and vagal stimulation, but the situation of CCK is confusing.

Most have argued that the combined effect of cholinomimetics and CCK is no more than additive. Preshaw et al [56] were unable to demonstrate potentiation of CCK stimulated protein secretion by urecholine; this is in accord with earlier work by Lin and Grossman [38] and Harper [15]. Konturek et al [31] have shown greater pancreatic protein secretion with urecholine and caerulein than with caerulein alone. Examination of his data reveals that the effects are almost exactly additive. There is no discussion of maxima. Nakamura et al [50] found, however, that methacholine with large doses of CCK produced a fall off in protein secretion which was much more rapid than that with CCK alone. No one using *in vivo* preparations seems to have reported supramaximal secretion with both stimulants given together.

Workers using *in vitro* methods [12] have claimed synergism on protein secretion between agents of the secretin and VIP class, which increase cyclic AMP levels, and those of the CCK and cholinomimetic class which act via calcium release or cyclic GMP accumulation. Synergism of this type has been claimed also, for example, Meyer et al [46] who used only two dogs but evidently a much larger *n*. More generally synergism has been denied, by those using *in vivo* preparations in dogs and cats [38]. An important consideration in this *in vitro* type of experiment is species. Many of the reportedly positive experiments have been done on rat pancreas which with that of the sheep [39] does increase protein secretion in response to secretin [51]. In these species, CCK-secretin protein synergism is hardly surprising and CCK cholinomimetic synergism is a possibility, but heretofore an unknown quantity. Others have been done in guinea pigs, a species in which the action of secretin on protein secretion is unknown, but in which, like the rat, CCK raises cyclic GMP [12]. As examples to back his argument for synergism, Gardner [12] cites work from conscious animals on fluid secretion (which he could not measure) rather than on amylase secretion which he did measure. Brown et al [6] could not detect protein potentiation with vagal stimulation. The evidence, therefore, that cholinomimetics sensitize the gland to the action of CCK is not good and there seems to be no evidence one way or the other on vagal stimulation. Bourde et al [5] did not measure protein secretion in their experiments with vagal stimulation in conscious dogs.

Does interruption of cholinergic influences on the pancreas alter the pancreatic responsiveness to CCK? This has proved to be as controversial as the secretin inquiry.

Singer et al [62], quoted above, concluded that atropine did not alter CCK stimulated protein secretion. Henriksen [20] likewise found no effect. Konturek et al [30] found that atropine depressed the action of small doses of CCK but not of large doses. This is of relevance to Henriksen's [20] work as he gave CCK as single boluses. Tiscornia et al [72] noted depression following both ganglionic blockade, vagotomy, and atropine. Rosenberg et al [58] found that atropine lowered CCK stimulated protein but had no effect on bicarbonate. Hong and Magee [27] were in agreement.

Debas et al [8] contended that truncal vagotomy diminished both the fluid and protein responses to intestinal stimuli and the bicarbonate response to 0.5 and 1 unit of secretin/kg/hr. The CCK or CCK octapeptide responses were not significantly altered at low doses of secretin. This seems to be a common pattern. Malagelada et al [43] found, in man, reduced enzyme secretion after vagotomy in response to low doses of CCK.

Our assessment of the data on CCK is that early preparations of CCK were sensitive to blockade by atropine due probably to a contained impurity. Preparations obtainable now seem to be slightly less effective at low doses after atropine or vagotomy. The work of Rosenberg et al [58] is an apparent exception to this since they used Swedish CCK but drainage of gastric juice into the duodenum could explain their results. CCK alone is a gastric-acid stimulant. The increased pancreatic enzyme secretion after antrectomy in response to CCK suggests this explanation. Our assessment must be tentative since in almost all instances secretin was used with CCK or caerulein and atropine and vagotomy can reduce both basal and secretin stimulated fluid, bicarbonate and protein (See above). In many instances it is impossible to determine whether or not this has been taken into account [29]. Another possible explanation for discrepant results is statistical in that as a general rule only three or four animals were used. If postvagotomy and postatropine depressions are small, these may well fail to reach significance (Singleton [64] and Debas et al [8]

[See above]). Singer et al [62] have subtracted the effect on secretin and have found that the effect of caerulein on the intact pancreas is uninfluenced by atropine. This raises the possibility that the pharmacologic characteristics of caerulein action are different from those of CCK.

A further explanation for discrepant results is in the technique for making the pancreatic fistula. In the Herrera type of preparation, most seem to have observed no depression of the CCK response by atropine or vagotomy. The results with the Thomas cannula have been variable. Using simple cannulation of the pancreatic duct, a technique which in many respects is the least physiologic nutritionally, but which might be calculated to be the least disruptive of the innervation of the gland, Magee et al [40] found in pigs with intact vagi, that atropine and ganglionic blockade did diminish the action of CCK. This experiment seems not to have been repeated following vagotomy. Atropine is, however, clearly without effect on the CCK stimulation of the transplanted pancreas. As might be expected, the blocking action is seen only with intact cholinergic innervation. Few have used ganglionic blocking agents on CCK or caerulein stimulation, but all who have, have found unequivocal depression [25, 27, 32]. The action of these agents on secretion from the transplanted pancreas does not seem to have been tried. The prediction would be no effect. It seems, therefore, that interruption of cholinergic innervation produces at most a slight depression of the action of exogenous CCK. Ganglionic blockade, however, produces marked depression. At the same time (see previous section) cholinomimetics seem to produce only an additive effect with CCK.

3. *Duodenal stimulants*

A depressant action of atropine and vagotomy on secretion stimulated from the duodenal lumen has been consistently observed.

Until 1943, it was assumed that secretin took care of water and bicarbonate secretion; the nerves, the enzymes. This was the view of Mellanby [45] whose secretin did not stimulate enzyme secretion. This view was fortified by the almost universal finding that atropine and vagotomy both reduced the enzyme response to feeding. The Leningrad school, for example (1902), found the fluid and enzyme responses to feeding greatly reduced by atropine. Thomas et al [71] verified this for enzymes. Wang et al [75] found, as had Farrell et al [9] before them, that the responsiveness of the transplanted pancreas to intraduodenal stimuli was uninfluenced by atropine. Hayama et al [19] found the daily secretion of fluid and enzymes to be reduced by vagotomy. Pincus et al [54] observed that chronic vagotomy reduced the enzyme response of the dog's pancreas to food by 80% and Henriksen and Rune [21] failed to elicit a significant response to intraduodenal HCl in conscious dogs. With added urecholine, the water and bicarbonate response to acid reappeared.

Many modern investigators have repeated these early experiments. It seems clear that atropine and vagotomy do reduce the effectiveness of duodenal stimulants of pancreatic secretion but it is not so clear that they abolish them. Hong and Magee [27] found the effect of HCl, peptone and oleic acid on enzymes greatly diminished by atropine and virtually abolished by ganglionic blockade. Hong et al [26] verified this in man, Fields et al [10], Wormsley [78] and Gamble et al [11] among others also have shown that vogotomy reduces the enzyme response to a meal in man. Singer et al [62] have found like Wang et al [75] that atropine does not reduce the effectiveness of either caerulein (which acts like CCK) or intraduodenal tryptophan on the transplanted pancreas and does reduce the effect of intraduodenal tryptophan, but not that of intravenous caerulein, on the intact gland. The postulate drawn from these experiments was that intestinal stimuli have two effects: the one to release CCK and secretin and the other to activate enteropancreatic nervous reflexes. The latter idea was raised by Pavlov's [52] school and has been repeated periodically since, notably by Thomas [70] and most recently by Singer et al [62].

Thomas et al [71] have found that during local block of the vagi the pancreatic response (protein and fluid) to intraduodenal peptone was depressed. They did similar experiments after thoracic vagotomy and noted reduced responses to intraduodenal peptone and, like Singer et al [63], an increase in the latency of the response. Hayama et al [19] have shown depressed daily protein and fluid secretion after vagotomy even in circumstances under which variations in gastric secretion were eliminated. Debas et al [8] found that truncal vagotomy reduced both basal and stimulated (intraduodenal amino acids) fluid, bicarbonate and protein secretion.

It seems clear, therefore, that interruption of the cholinergic nerves has a depressant action on the protein and fluid secretion in response to meals indicating that either there is a cholinergic mechanism for the release of CCK and secretin or a vagally mediated facilitation of their action on the gland. A pancreatic mechanism is more likely for secretin (Henriksen et al [21] does not agree) since the action of exogenous secretin is more obviously affected by anticholinergics than is that of CCK. Modlin et al [47] have shown that atropine slightly depressed the serum CCK plateau attained following intraduodenal sodium oleate, but greatly depressed pancreatic protein secretion. This indicates cholinergic involvement in the duodenal release of CCK and also either cholinergic sensitization to CCK or direct cholinergic stimulation of the acini but does not tell us the source of the latter, that is, whether vagal or local enteropancreatic reflexes. The failure (Hong and Magee [27]) to find any effect of atropine or C_6 (hexamethonium chloride) on pancreatic secretion stimulated with CCK or secretin in animals after vagotomy favors vagal influences over local reflexes and so does the undoubted reduction in the effectiveness of intraduodenal stimulants following vagotomy [8, 21, 71].

It has been stated above that vagal stimulation will cause enzyme and fluid secretion especially in anesthetized pigs, cats and rats. Holst et al [25] has shown that vagal stimulation of fluid secretion is abolished by ganglionic blocking agents, both he, in pigs, and Lenninger et al [35] in cats, have shown that this response is not atropine sensitive but the augmentation of enzyme secretion is. In the dog, the very small fluid response, the augmented secretin response and the greater enzyme response following vagal stimulation are atropine sensitive [23]. These experiments, however, do not tell us whether or not vagal stimulation releases pancreatropic hormones. Lenninger et al [35] have concluded from cross-circulation experiments in cats that vagal stimulation acts directly on both acinar and duct cells. Hickson [23], Magee et al [42] and Magee and Sullivan [41] in experiments in which removal of the duodenum did not reduce vagally stimulated secretion indicate a direct action on fluid secretion and the latter on enzyme secretion also.

The above evidence indicates a clear difference between pigs and cats, and dogs in the response of duct cells to the vagi but gives no indication that vagal stimulation releases pancreatropic hormones. Indeed, Guzman et al [14] working with anesthetized dogs have obtained the expected pancreatic response to vagal stimulation, but no increase in either serum secretin or CCK. Gastrin was, however, elevated and the effect of vagal stimulation on the pancreas was greatly reduced by removal of the antral mucosa; their conclusion is implicit in the results of Preshaw et al [57] to explain the pancreatic stimulation caused by sham feeding in dogs, but is excluded in pigs by Hickson [23] who removed the antrum. Rosenberg et al [58] agreed with Preshaw et al [57] in that antrectomy and anteroneurolysis reduced insulin induced enzyme secretion by 80%, but Lenninger et al [35] in cross-circulation experiments in cats found no humoral component to vagal stimulation of pancreatic secretion. Guzman et al [14] dismissed the elevation in VIP which Holst et al [25] also had noted under similar circumstances in pigs. Holst et al had found no elevation in secretin either. Larsson et al [33] have noted VIP containing nerves in a variety of species and propose that VIP inergic nerves rather than secretin liberation explain the atropine resistance to vagal stimulation in pigs and perhaps cats, which have similar innervation. In both studies the action of secretin was clearly augmented by vagal stimulation but was once again atropine sensitive in the dog, but not in the pig or cat.

It seems, therefore, that intact cholinergic innervation is necessary for optimal but not for all pancreatic responsiveness to intestinal stimuli. There is no evidence that vagal stimulation liberates either secretin or CCK. In the case of CCK the facilitatory action of the vagi seems to be largely duodenal, but in the case of secretin could be pancreatic also since exogenous secretin is augmented by cholinergics. The action of ganglionic blockers makes a noncholinergic nervous facilitating factor possible in the case of CCK.

Local anesthetization of the duodenal mucosa has been found by a series of workers (Schapiro et al [60], Slayback et al [65], Hong and Magee [27] etc) to render the pancreas less sensitive to intraduodenal stimuli with the possible exception of HCl. A possible explanation for this is nervous receptor mediation of duodenal hormone secretion or reflex facilitation of their action. Some local anesthetics (oxethazaine) on application to the mucosa stimulate secretion before evidently paralyzing the appropriate mucosal endings.

The experiments with local anesthetization of the mucosa, like those with anticholinergics and ganglionic blockade, have not reached the stage at which one can separate an intrinsic nervous mechanism for CCK release from a duodenopancreatic reflex connection, local or vagal, but parasympathetic involvement in either or both the release of CCK and the response of the pancreas to it is backed by a good body of evidence. The vagal trunks play a part in this, but whether or not intrinsic duodeno-pancreatic reflexes exist or can exist without the vagi is unclear. The gland, however, will respond to intestinal stimuli without the vagi, for example, when transplanted.

The work of Singer et al [62] with atropine and on response latency [63] is not in favor of any nervous mechanism for CCK or secretin release intrinsic or extrinsic but it does not distinguish between long vagal or duodenopancreatic reflexes. To resolve these problems the decisive experiments do not seem to have been done, that is, does local anesthetization of the mucosa depress the secretion of the transplanted pancreas or the CCK serum levels following intraduodenal stimulation or does duodenal local anesthetization depress the pancreatic response in vagotomized animals? Thambugala et al [68] and Tiscornia et al [73] have claimed that local anesthetization of the duodenum interferes with the action of secretin on the intact pancreas, but the observation of the former was in one animal only and the latter found augmentation of the action of CCK which is different from the action of local anesthetics on enzyme secretion following intraduodenal stimuli. The action of HCl in the duodenum on pancreatic secretion is not depressed by local anesthetics but is by atropine.

It is very curious that, despite almost identical experiments and results and in many cases identical experimentors, the pharmacologic construct, for a long time, accepted as existing between antral receptors and the gastrin secreting cell has not been seriously considered in the case of secretin and pancreozymin and, on the other hand, reflexes between gastric antrum (hormone source) and secreting mucosa (hormone target) have received no serious consideration either but have long been the vogue in pancreatic physiology.

Singer's et al [63] evidence is indirect, but against an intramucosal cholinergic mechanism, such as has been described for the stomach. The transplanted pancreas cannot distinguish between long vagal or short local reflexes between duodenum and pancreas. It is our view that all three of these possibilities still await decisive experiments.

Conclusions

How much is left of the original hypothesis?

The evidence is good that CCK and secretin do cause pancreatic secretion and so do the vagi directly at least in pigs and cats. It is substantial for the contention that cholinomimetics and the vagi augment the action of secretin, but much less so for CCK. It is clear that duodenal stimulants are more effective on protein and water when the cholinergic innervation of the intestine is intact because either the gland or the cells which produce secretin and CCK are more responsive to intestinal stimuli. There is not enough evidence to distinguish between these alternatives at the moment. It is clear that although nerves facilitate the response to intraduodenal stimuli they are not essential for it. There is no substantial evidence, direct or indirect, that the vagi can or do release pancreatropic hormones; local anesthetic sensitive mechanisms for the release of these hormones are present in the duodenum.

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Prophylactic Mastectomy

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Abstract

Prophylactic mastectomy may be indicated in certain high risk patients such as those with a strong familial history of breast cancer. This report identifies these cases and attempts to clarify the indication for prophylactic mastectomy. Cases in several categories are presented and discussed.

In spite of recent efforts at earlier detection through public education and screening, breast cancer remains a leading cause of death in young women. It also appears as though the incidence is increasing (1). To improve survival, we must not only concentrate on treating the patient who has an invasive breast cancer but every effort must be made to treat this disease at an even earlier stage.

A famous surgeon once said, "If all women were to have their breasts removed at puberty, breast cancer could be eliminated." While this approach is rather drastic and unacceptable in our breast oriented society, there are indications for prophylactic mastectomy. Since it is now possible to reconstruct acceptable appearing breasts (2), the concept of surgical prophylaxis may not be as radical as it once seemed. One in thirteen women is expected to develop cancer of the breast. This report will attempt to identify those patients who are at an even higher risk and to clarify the indications for prophylactic mastectomy.

Case Reports

Case 1: A 46-year-old nurse underwent a left modified radical mastectomy as treatment for a 0.5 cm infiltrating duct cell carcinoma which had been detected by a cluster of microcalcifications on annual mammography. A contralateral breast biopsy demonstrated marked proliferative changes similar to those present in the breast resected for carcinoma. The patient's mother had died of breast cancer and one maternal aunt and two cousins also had the disease. The remaining breast was large, ptotic and nodular (Fig. 1).

One year following the mastectomy, a first stage left breast reconstruction using a subpectoral inflatable implant was carried out together with a right total mastectomy and simultaneous reconstruction. The implant was placed under the pectoralis muscle and was protected inferiorly with a dermal flap created from the residual skin of the inferior portion of the breast. The remaining nipple was divided into two and banked in the groin. Three months later, the nipples were transplanted to the reconstructed breasts (Fig. 2).

The prophylactic mastectomy specimen did not contain carcinoma, but, because of duct cell hyperplasia and intraductal papillomatosis with marked cell atypia, it was considered a precancerous mastopathy (Fig. 3).

Case 2: A 49-year-old woman underwent a left modified radical mastectomy for a 3.5 cm intraductal carcinoma with invasion in January 1980. Four years earlier, a biopsy of that same breast had demonstrated sclerosing adenosis with extensive microcalcifications. In 1977, a cyst of the left breast had been aspirated. A contralateral breast biopsy (random) at the time of the mastectomy showed intraductal hyperplasia with cellular atypia, sclerosing adenosis and microcalcifications. The findings were similar to those noted in the resected breast. The remaining breast was pendulous and nodular and the patient was concerned about the development of a new breast cancer because she had gross cystic disease and felt uneasy about repeated examinations, aspirations and mammographies which would be required to follow her remaining breast (Fig. 4a).

Eight months after the mastectomy, a first

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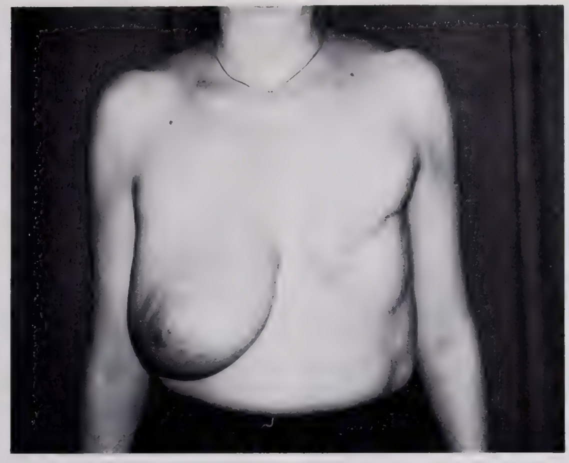


FIG. 1. One year post-modified radical mastectomy.

stage left breast reconstruction was performed using a subpectoral inflatable implant as well as a right total mastectomy with simultaneous first stage reconstruction. The remaining nipple/areola complex was divided into two, banked in the groin and transplanted to the reconstructed breasts three months later (Figs. 4b & c).

The prophylactic mastectomy specimen did not contain carcinoma but the microscopic findings were reported as precancerous mastopathy.

Case 3: A 55-year-old psychiatrist underwent a left modified radical mastectomy as treatment for a carcinoma of the breast in November 1976. Because there was one positive axillary lymph node, adjunctive chemotherapy was administered for one year. In April 1978, reconstruction of the left

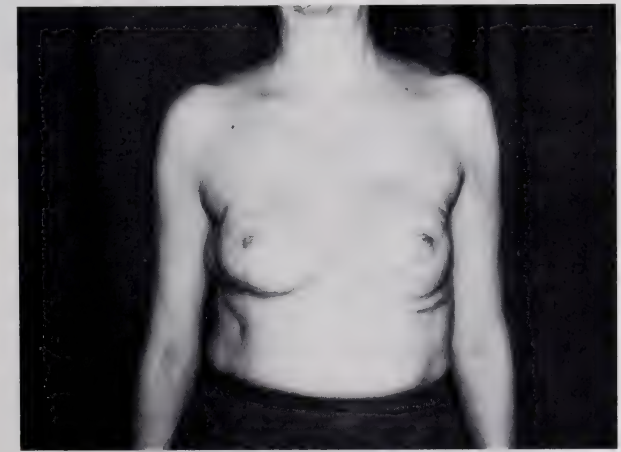


FIG. 2. One year post-right prophylactic mastectomy and reconstruction in 2 stages.

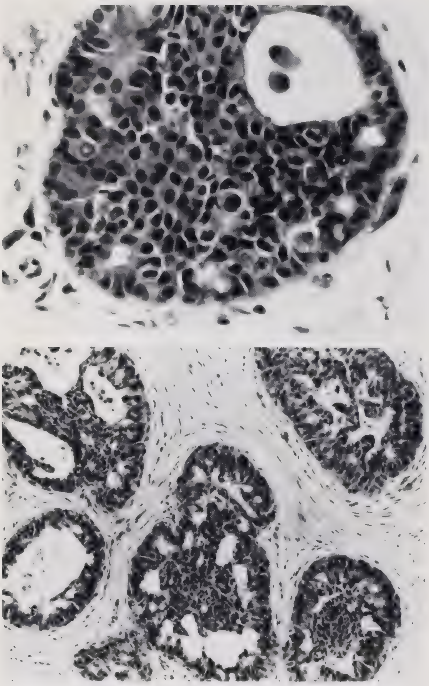


FIG. 3a. Right mastectomy specimen. Note duct cell hyperplasia with cellular atypia. H + E ×460. 3b. Note intraductal papillomatosis with cellular atypia. H + E ×130.

breast was performed. Because the patient was concerned about developing a carcinoma of the remaining breast, she requested a prophylactic mastectomy. In November 1979 a right total mastectomy was performed with immediate reconstruction to achieve mammary symmetry. Lobular carcinoma in situ was present in the resected specimen.

Case 4: A 35-year-old woman was referred for consideration as a candidate for bilateral subcutaneous mastectomies. There was a history of having had multiple operations for fibroadenomata of both breasts. The most recent biopsy revealed some atypical cells. A paternal first cousin had breast cancer.

On examination, the breasts were small, slightly ptotic and multinodular with scarring from prior operations (Fig. 5a). Prophylactic bilateral subcutaneous mastectomy was discussed with the patient and her husband. The limitations and possible complications were pointed out but no decision was made at that time.

One year after the examination the patient's physician discovered a new nodule. This proved to be an infiltrating duct carcinoma. A left modified radical mastectomy was performed and the nipple banked in the groin for subsequent reconstruction. On pathologic examination, the left breast showed marked proliferative changes including adenomatosis, papillomatosis, blunt duct adenosis with focal cellular atypia, apocrine metaplasia, a papilloma of a large subareolar duct and microcalcifications in addition to carcinoma.

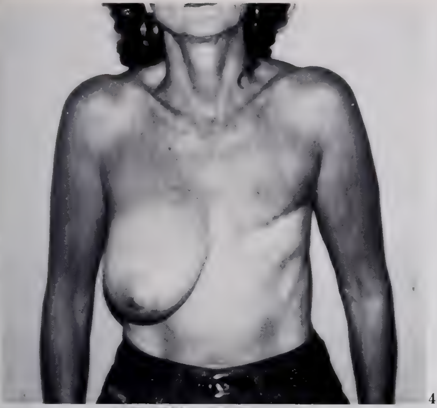
Six months later, a right total mastectomy with nipple banking was performed prophylactically. This breast contained a plethora of benign pathologic findings (Fig. 5b).

Nine months later, bilateral breast reconstruction was carried out utilizing silicone implants inflated with saline and placed subpectorally. Four months later, the banked nipples were transferred from the groin. The patient has done well postoperatively and is pleased with the reconstruction (Fig 5c).

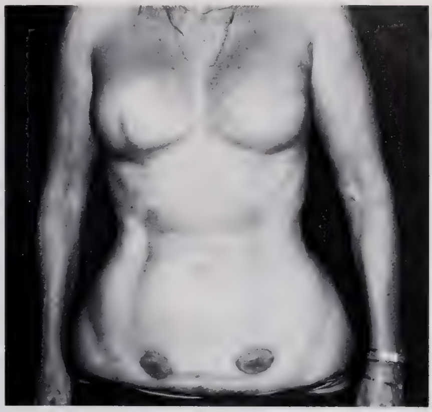
Case 5: A 30-year-old female had a left partial mastectomy performed for cystic disease at age 27 and removal of a fibroadenoma from the same breast. Her mother underwent bilateral radical mastectomies as treatment for breast cancer at age 40 and 42. A maternal aunt died at the age of 39 of metastatic breast carcinoma as did a paternal aunt. There were also cousins on both sides of the family with breast cancer. The patient had moderately severe cancerophobia and requested prophylactic mastectomies.

On examination, her breasts were large, ptotic, multinodular and somewhat tender (Fig 6a). Bilateral total mastectomies with simultaneous reconstruction were performed. The result was satisfactory and the patient appears relieved of her anxiety (Fig. 6b). Pathologic examination revealed fibrocystic disease.

Case 6: This 49-year-old single female underwent right breast biopsies in 1971 and 1977 with the findings of fibrocystic disease of the breast. In the course of follow-up, additional nodularity became apparent beneath the surgical scar in the previously biopsied area in the upper outer quadrant of the breast. In November 1978, the firm areas were excised and lobular carcinoma in situ was diagnosed. The patient sought several opinions as to management of this problem and she elected to have bilateral total mastectomies with immediate reconstruction. This was carried out in January 1979. Additional noninvasive carcinoma



4a



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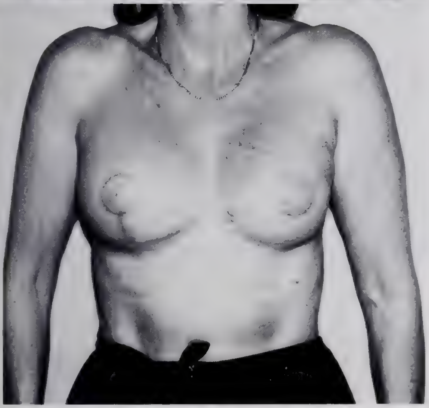


4c

FIG. 4a. Eight months after left modified radical mastectomy. 4b. Three months post-right prophylactic mastectomy with simultaneous bilateral first stage reconstruction with silicone implants, division of right nipple into two and banking on the lower abdomen. 4c. Three months post-nipple transplantation.

was found in the right breast. Fibrocystic disease of the left breast was present. Both nipples had been banked in the groin and these were subsequently transplanted to the breasts.

Background

In an effort to determine whether certain benign breast lesions have a high malignant potential, Bader et al reviewed a large number of breast biopsies (3). A significant number of patients with extensive papillomatosis or large ductal hyperplasia subsequently developed carcinoma of the breast. They concluded that these patients were at high risk (at least 13 to 15 times the normal incidence and a high percentage of bilaterality) and should have bilateral prophylactic mastectomies. Leis has followed 28 patients with ductal epithelial hyperplasia with marked atypia for 15 or more years (4). Twenty-five percent have developed invasive cancer in the same breast and 7% in the contralateral breast. Ashikari et al have reported a similar experience in 572 patients (5). Leis feels that prophylactic mastectomy should be considered in these cases if the emotional response is extreme or a factor such as a significant family history indicates an even higher risk (6).

While many studies have shown a relationship between fibrocystic disease and carcinoma (7), the most significant lesions appear to be hyperplasias with cellular atypia (8–11).

Pennisi encountered a 6.1% incidence of obscure breast carcinoma in subcutaneous mas-

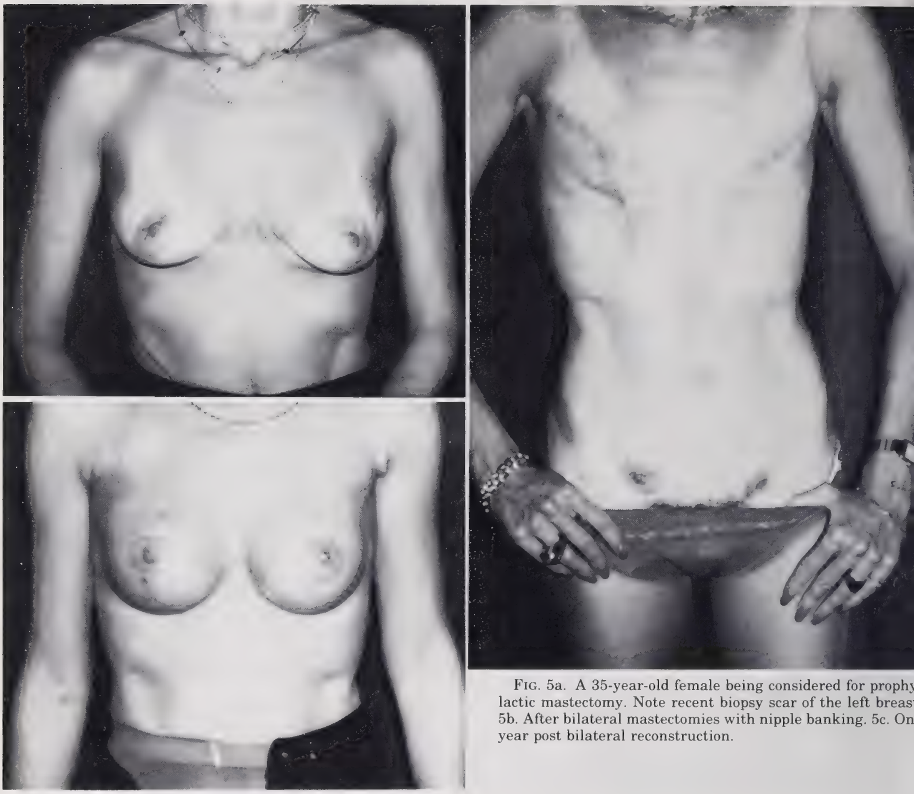
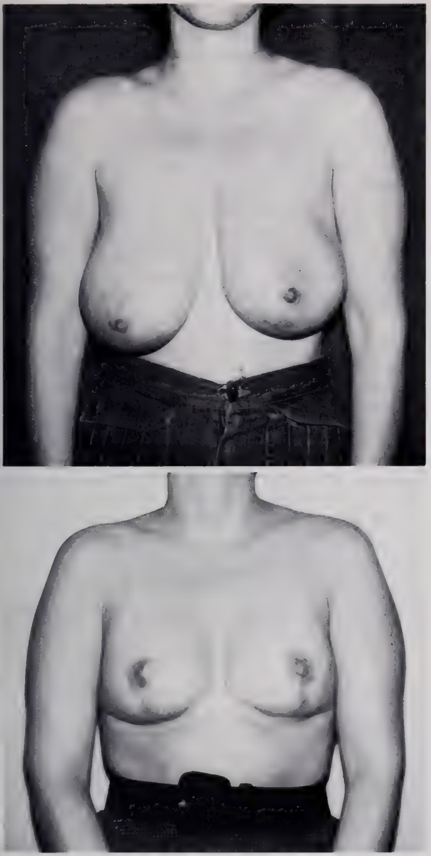


FIG. 5a. A 35-year-old female being considered for prophylactic mastectomy. Note recent biopsy scar of the left breas 5b. After bilateral mastectomies with nipple banking. 5c. On year post bilateral reconstruction.

tectomies and a 15.4% incidence of lobular neoplasia or carcinoma in situ for a combined incidence of 21.5% (12). These were small lesions found by the pathologist on careful examination. He also surveyed a number of surgeons who reported a 6% incidence in 1,385 patients. Also, there was a 0.5% incidence of breast cancer which developed after the subcutaneous mastectomy was performed. Pennisi concluded that only patients who demonstrate moderate to severe fibrocystic disease proven by surgical biopsy with microscopic features of sclerosing adenosis, papillomatosis, intraductal hyperplasia, microcystic disease or even macrocystic disease should be operated on.

It has long been recognized that there is an increased risk of developing carcinoma in the remaining breast after mastectomy (13). Using preoperative mammography, Egan found an incidence of 3%–4% of occult carcinomas in the contralateral breast (14, 15).

Urban noted that a large number of his patients developed a carcinoma of the remaining breast and this prompted the introduction of routine contralateral biopsy at the time of the initial mastectomy (16). Of these biopsies, 12.5% were positive for carcinoma and 9.2% showed significant atypia. Pressman reported finding carcinoma in 14% of the opposite breasts of which 12% were found on a truly random basis (17). Atypical epithelial hyperplasia was present in 12% of the specimens. Leis states that while the exact incidence of bilaterality is not known it is higher than previously thought. In a series of 101 high risk



6a

6b

FIG. 6a. A 30-year-old female with a strong familial history of breast cancer. Note depression of left upper outer quadrant at site of partial mastectomy. 6b. One year after prophylactic mastectomy with simultaneous reconstruction.

patients who underwent a contralateral prophylactic mastectomy, there was an incidence of 16.8% carcinoma in the resected breasts (18). Because of this finding, he recommends prophylactic mastectomy of the remaining breast in selected high risk patients (19).

While some women may be reluctant to lose the remaining breast, many express fear of developing a new cancer which may be found in a more advanced stage than the one for which they were originally successfully treated. They are anxious about repeated physical examinations and the periodic mammographies which are required. When the remaining breast is large or ptotic, a reduction mammaplasty or mastopexy is required to achieve symmetry after unilateral breast reconstruction.

After reduction mammaplasty, detection of carcinoma by physical examination or mammography may be more difficult because of the additional scarring in the breast. Extending the reduction to include all of the breast tissue and simultaneously reconstructing the breast with a silicone implant adds little to the procedure and assures almost complete removal of the mammary tissue. Of course, there is the possibility of capsular contracture around the implant but this risk must be weighed against the possibility of developing carcinoma. It is for these reasons that prophylactic mastectomy was perfomred in this high risk group of patients.

In addition, symmetry is more readily achieved if implants are placed bilaterally rather than attempting to match the contralateral breast to the reconstructed one.

Technical Considerations

To completely prevent the development of cancer, all of the breast tissue must be removed. Subcutaneous mastectomy, as commonly performed, shells out varying amounts of breast tissue leaving an empty sack of overlying skin including the nipple and areola. In order to preserve circulation to the skin, the subdermal plexus must be protected. This requires leaving thick residual skin flaps so that a considerable amount of breast tissue remains which reduces the prophylactic benefit of the procedure (20). In addition, the esthetic result leaves much to be desired. Fibrous capsular contractures are common when implants are placed under the skin flaps, leaving the patient with hard, globular, unattractive and sometimes painful breasts. Alternatives to this approach have been described which provide for a more thorough removal of the mammary gland and more satisfactory esthetic results (21). Simple mastectomy with secondary reconstruction using silicone implants placed subpectorally or a total mastectomy with simultaneous reconstruction are recommended. Whenever silicone implants are used, however, capsular contracture can occur, an important consideration in deciding on prophylactic mastectomy. The incidence of this complication has been reported as from 5%–25%. In some cases the contracture can be relieved by additional surgery. At the time of breast removal, the specimen is sectioned by the pathologist to make certain that no gross carcinoma is present, since at this point the operation can be converted into a modified radical mastectomy if an invasive lesion is found. Any enlarged axillary lymph nodes can also be biopsied.

The nipple-areola complex must not be preserved in a breast which has an invasive carcinoma because of the possibility that microscopic cancer may be present (22, 23). When preserving the nipple-areola complex as a part of a prophylactic operation, biopsies of the central breast tissue and from within the nipple itself are obtained. Currently we are not encouraging nipple banking for most cases since these nipples become depigmented and scarred.

Discussion

The indications which have evolved for performing a prophylcatic mastectomy are:

1. History of prior mastectomy for breast cancer
2. Breast biopsy demonstrating precancerous mastopathy
3. Repeated breast biopsies with
    a. resulting breast deformity
    b. progressive fibrocystic disease
4. Strong family history
5. Severe cancerophobia, particularly with a family history of breast cancer.
6. Lobular carcinoma in situ

Cases 1–4 are patients who were predictably at risk for developing a second breast cancer because they already had a breast cancer. These women were all under 50 which places them in an even higher risk category. In general, we are less likely to recommend prophylactic mastectomy in older women.

In broadening our criteria, we recommended bilateral mastectomies for the fourth patient because she had multiple breast biopsies and cellular atypia was reported. The evidence for the malignant potential of those histologic findings considered to represent precancerous mastopathy has already been presented. This patient declined the recommendation for an operation and did go on to develop an invasive cancer. The fifth patient is an example of a truly prophylactic operation in a woman at an enormously high risk.

Finally, a word about lobular carcinoma in situ. There has been disagreement about its management because it is so frequently a bilateral disease (24,25). Performing a unilateral mastectomy does not protect against the development of a contralateral invasive cancer which statistically occurs as frequently as on the side where the diagnosis was originally made in as many as one third of the patients. Yet, to recommend bilateral mastectomies has seemed extreme particularly since it may take twenty years for the invasive cancer to become apparent. The alternative to surgery is a lifetime of frequent physical examinations and mammographies, watching and waiting for an invasive cancer to become apparent. Bilateral total mastectomies with immediate reconstruction offer the certainty of cure with minimal deformity. It is important to emphasize that the prophylactic operation should be a true cancer operation, not a subcutaneous mastectomy. All of the breast tissue must be removed and this entails a total mastectomy with the proper development of skin flaps.

Performing a radical or modified radical mastectomy has been the traditional approach to treating invasive breast cancer. Recently, the alternative of preserving the breast by performing a partial mastectomy with axillary node sampling followed by primary radiation therapy has been reported to achieve similar rates of local control and cure in selected patients (26). Radiation therapy cannot be recommended as a prophylactic treatment because the development of new cancers in the previously irradiated breast tissue is an expected sequelae to this treatment approach.

Conclusions

Prophylactic mastectomy is recommended for patients at a particularly high risk for the development of an invasive breast cancer. For women who have had a mastectomy and who are to undergo breast reconstruction, it is a logical approach to managing the opposite breast providing excellent mammary symmetry with bilateral implants. Since good cosmetic results can now be expected with bilateral mastectomies and reconstruction, the indications can be broadened to include other women at risk.

Acknowledgments

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Torsade De Pointes caused by Disopyramide and Hypokalemia

Paul Schweitzer, M.D. and Herbert Mark, M.D.

Abstract

An unusual double arrhythmia, consisting of disopyramide induced torsade de pointe and atrial tachycardia caused by digitalis toxicity and hypokalemia, occurred in a patient with severe three vessel coronary artery disease and a ventricular aneurysm. The arrhythmias were successfully treated with bretylium, propranolol and potassium.

A review of eleven reported cases of ventricular tachycardia attributed to disopyramide indicates that additional disorders are often present in these patients and may predispose to the development of this arrhythmia. Administration of disopyramide should be avoided in the presence of these conditions, which include mitral valve prolapse, the bradycardia-tachycardia syndrome, hypokalemia and drug effects, all of which may cause prolongation of the QTc interval.

Torsade de pointes (TDP) is an acute atypical ventricular tachycardia characterized by constant change in the amplitude and the direction of the QRS complex (1–3). Drugs that prolong the QT interval are among the most frequent causes of TDP (2–4). A patient in whom TDP was probably caused by a combination of disopyramide and hypokalemia is the subject of this report. This patient also had digitalis toxicity, which produced an unusual double arrhythmia with TDP and atrial tachycardia.

Case Report

The patient was a 46-year-old man with a history of myocardial infarction and hypertension. Severe three vessel coronary artery disease and a ventricular aneurysm had been demonstrated previously by angiography. Short runs of ventricular tachycardia not associated with symptoms had been recorded in the past. Medications given to the patient included digoxin 0.25 mg, furosemide 40 mg and disopyramide 600 mg per day for the preceding three months. On the day of admission, the patient complained of palpitation and dizziness lasting for one hour. Physical examination revealed cardiomegaly and a third heart sound. No other abnormalities were noted. Positive laboratory findings included a serum potassium of 3.2 mEq/l, elevation of blood urea nitrogen to 28 mg% and a serum creatinine level of 2.1 mg%. On chest x-ray lung fields were clear and cardiomegaly was present.

The admission ECG revealed atrial tachycardia (150/min) which was interrupted by TDP (Fig. 1A), evidence of anterior myocardial infarction, and a prolonged QT interval (QTc 0.52) (Not shown). The TDP repeatedly degenerated into ventricular fibrillation. Each episode was successfully terminated with DC counter shock, but sinus rhythm was maintained only briefly, and the pattern of alternating atrial tachycardia and TDP recurred each time. Initial therapy with intravenous lidocaine was not effective. Administration of bretylium (300mg. IV) was started, after which the paroxysms of TDP became shorter and less frequent, and some brief episodes of ventricular fibrillation converted spontaneously to atrial tachycardia (Fig. 1B–D). Because the TDP was not completely controlled with bretylium and because the atrial tachycardia persisted (2A), two milligrams of propranolol were administered intravenously. This produced 2:1 AV block (Fig. 2B). At this time, hypokalemia was reported by the laboratory and intravenous potassium was administered. Infusion of potassium promptly slowed the atrial rate to 125/min and simultaneously restored 1:1 AV conduction (Fig. 2C). Twenty-five minutes after initiation of potas-

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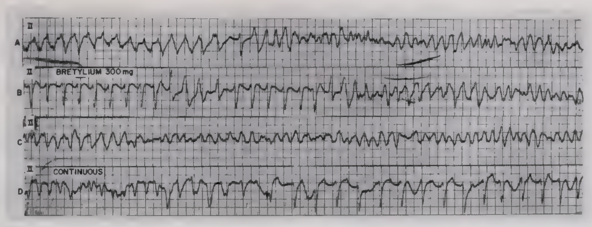

FIG. 1. (Lead II) is showing TDP before and after the administration of 300 mg of bretylium. A) TDP. B) Atrial tachycardia interrupted by TDP which is spontaneously converted into atrial tachycardia (C,D).

sium, the atrial tachycardia terminated and was replaced by sinus rhythm (Fig. 2D). Serum digoxin level taken on admission was 3.8 ng/ml. After control of these complex arrhythmias, the patient made an uneventful recovery.

Discussion

There were several possible causes for the TDP in this patient. The two most important were assumed to be disopyramide toxicity and hypokalemia (2–4). Because the patient had been taking disopyramide for three months without side effects, it does not seem likely that the drug alone was responsible for the arrhythmia. The most likely contributing factor for the arrhythmia was hypokalemia, which is a known case of TDP (3, 4).

The role of coronary artery disease and the ventricular aneurysm in the pathogenesis of TDP in this patient is more difficult to evaluate. Ischemic heart disease rarely causes TDP (5), while arrhythmias in patients with ventricular aneurysm usually take the form of a uniform ventricular tachycardia.

Recently, however, Horowitz et al (6) reported TDP in patients with normal QT interval. The arrhythmia occurred spontaneously or was induced by programmed stimulation and was not related to drugs or electrolyte imbalance. Because our patient had delayed repolarization and the arrhythmia was transient, we believe that it fulfills the criteria of a "typical" TDP due to prolonged repolarization. Finally, the arrhythmia could be related to digitalis toxicity. While cardiac glycosides do not cause TDP (3, 7), a possible interaction among digoxin, disopyramide or hypokalemia in the development of TDP cannot be excluded.

Attempts to control, TDP in this patient led to administration of bretylium, propranolol and potassium. The use of bretylium was based on the observation of Vander Ark et al (8) that the drug can be effective in the management of quinidine syncope. Bretylium did have a partial effect in this patient because the paroxysms of TDP became less frequent, were of shorter duration, and no longer required defibrillation. The second

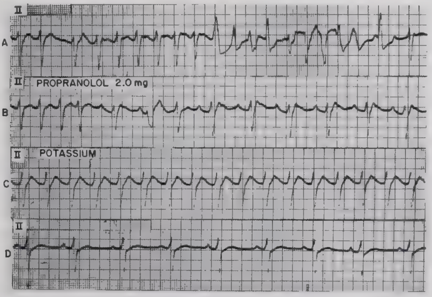

FIG. 2. (Lead II) shows the effect of propranolol and potassium on TDP and atrial tachycardia. A) Short run of TDP. B) Atrial tachycardia with 2:1 AV Block. C) Atrial tachycardia. D) Normal sinus rhythm.

medication used in this patient, propranolol, was administered in an effort to control both TDP and the atrial tachycardia. Propranolol probably contributed to the suppression of TDP and by acting on the AV node caused 2:1 atrioventricular block and slowed the ventricular rate.

The patient also received potassium, which converted the atrial tachycardia to sinus rhythm. This prompt action of potassium and the high level of serum digoxin obtained on admission indicate that the atrial tachycardia was most likely a manifestation of digitalis toxicity.

Disopyramide induced TDP was first reported by Casedevant and colleagues (4) in a patient with hypokalemia, who probably also had a bradycardia-tachycardia syndrome. The arrhythmogenic effect of disopyramide has subsequently been confirmed by others (4, 9−14). In a review of the literature, we found eleven cases of ventricular tachycardia related to oral administration of disopyramide and have added our own (4, 9−14) (Table I). In all but one patient, the QTc interval was longer than 0.45 second (Table I). The arrhythmia induced by disopyramide was diagnosed by various observers as atypical ventricular tachycardia (10), torsade de pointes (4), ventricular fibrilloflutter (11, 12), and ventricular tachycardia resembling that caused by quinidine (9). This latter finding was not unexpected, because of the similar electrophysiologic properties of these two drugs (15).

The underlying heart disease in patients with disopyramide induced ventricular tachycardia included rheumatic heart disease, coronary artery disease, hypertension, cardiomyopathy and mitral valve prolapse. The patient reported by Casedevant et al (4) and two additional patients (11) had a bradycardia-tachycardia syndrome. Congestive heart failure was present in three patients. The indication for administration of disopyramide in these patients also varied. It was used in five because of the presence of ventricular tachycardia and in three others for control of ventricular premature beats. Atrial extrasystoles, atrial fibrillation or atrial tachycardia were considered the indication for disopyramide in four cases.

The dose of disopyramide at which ventricular tachycardia developed was in the usually accepted therapeutic range in all but one patient (10) who received 2400 mg of disopyramide per day. However, the administration of recom-

TABLE I

AUTHORS	YEAR	CLINICAL DIAGNOSIS	INDICATION	DOSE MG.	DURATION	QTc	KmEq/L	CONCOMITANT THERAPY
Casedevant Et Al	1975	Hypertension BTS	?AF	600	5M	0.76	3.0	Digitalis
Frieden	1978	CHF	VT	300	2D	0.44	4.2	Digitalis & Furosemide
Meltzer Et Al	1978	CAD	VT	2400	1D	0.52	4.5	Phenytoin
Dhurandhar Et Al	1978	BTS	APC's	600	5D	0.58	4.8	
Dhurandhar Et Al	1978	BTS	VPC's	400	3M	0.58	4.0	
Dhurandhar Et Al	1978	No HD	VPC's	600	1M	0.58	4.2	
Nicholson Et Al	1979	RHD	AT	900	8H	0.56	4.2	Digitalis
Nicholson Et Al	1979	RHD	AT	600	1M	0.54	4.7	Digitalis
Nicholson Et Al	1979	MVP	VT	600	6D	0.72	3.7	Thiazide, Potassium
Tri	1979	CCMP	VT	400	18D	0.65		Digitalis, Diuretics ?
Lo Et Al	1980	CAD, CHF	VPC's	400	9D	0.46	4.2	Digoxin, Hydralazine
Present Case	1980	CAD, VA	VT	600	3M	0.52	3.2	Digitalis - Furosemide

BTS = Bradycardia Tachycardia Syndrome; CHF = Congestive Heart Failure; NoHD = No Heart Disease; RHD = Rheumatic Heart Disease, MVP = Mitral Valve Prolapse; CEMP = Congestive Cardiomyopathy; VA = Ventricular Aneurysm; AF = Atrial Fibrillation; VT = Ventricular Tachycardia; APC's = Atrial Premature Beats; VPC's = Ventricular premature beats; AT = Atrial Tachycardia; M = Month; D = Days; H = Hours.

mended doses does not exclude the possibility that the plasma level of disopyramide is elevated. Lo et al (14), recently reported a patient with congestive heart failure who despite taking 100 mg of disopyramide four times a day had an excessively high plasma level of disopyramide. These authors assumed that the toxic plasma level of disopyramide resulted from impaired liver and renal function. Because plasma levels of disopyramide were not measured in the majority of patients who developed ventricular tachycardia, the incidence of its toxic level in these patients remains uncertain.

Our analysis of the reported cases (Table I), suggests that in some patients, at least, the ventricular tachycardia was caused by other factors along with disopyramide. Two patients who developed ventricular tachycardia after the administration of disopyramide also had low serum potassium, which itself can cause TDP (2, 3).

Three patients with disopyramide induced ventricular tachycardia had a bradycardia-tachycardia syndrome and the arrhythmia occurred when the heart rate was slow. Bradycardia is known to predispose to the development of TDP (2, 3). In addition, disopyramide probably accentuates the arrhythmogenic effect of bradycardia by further impairing sinus node function (16).

In another patient with mitral valve prolapse disopyramide aggravated the preexisting ventricular arrhythmia, a finding that is not surprising because TDP can be a complication of mitral valve prolapse (17, 18). The importance of hepatic and renal function in contributing to toxicity of disopyramide has already been mentioned (14).

Not infrequently disopyramide is administered concomitantly with other drugs, especially digitalis. Seven patients who developed ventricular tachycardia after disopyramide also received digitalis. Whether digitalis can potentiate the arrhythmogenic effect of disopyramide cannot be answered because the interaction between digitalis and disopyramide is not clear. Doehring (19) and others (20) have shown that disopyramide does not increase the serum digoxin level but this observation does not exclude the possibility of a drug interaction or that digitalized patients may have an increased risk of developing disopyramide induced ventricular tachycardia. The ability of other antiarrhythmic drugs to potentiate the adverse effect of disopyramide was recently emphasized by Ellrodt and Singh (21).

Another practical question is whether patients who develop ventricular tachycardia after quinidine are also at high risk for disopyramide induced arrhythmias because both drugs cause delayed depolarization and prolongation of the QT interval. The answer to this question is not clear. Two patients with disopyramide related ventricular tachycardia also experienced quinidine induced ventricular tachycardia. Disopyramide was given to control (11, 13) ventricular arrhythmias in one of these patients and to suppress atrial premature beats in the second. On the other hand, another patient with an atrial arrhythmia who developed ventricular tachycardia after quinidine was treated with disopyramide alone and suffered no complications (22). In three additional patients who received quinidine and disopyramide, the latter alone caused ventricular tachycardia (9–11). The arrhythmia in one of these patients was related to toxic doses of disopyramide (10). These limited experiences suggest that disopyramide should be administered cautiously to patients with quinidine syncope.

An unusual feature of our patient was the combination of TDP and atrial tachycardia. The former arrhythmia not only occurs more frequently in patients with slow heart rate, but can be effectively controlled by fast heart rate (2). In other words, the tachycardia did not protect this patient from TDP.

In summary, this review supports the assumption that underlying heart disease, electrolyte imbalance and the concurrent administration of other drugs may play an important role in the pathogenesis of disopyramide induced torsade de pointes. Furthermore, there are patients in whom the arrhythmia has multifactorial origin. Based on our review of published reports, the use of disopyramide should be avoided in patients with hypokalemia, bradycardia-tachycardia syndrome and mitral valve prolapse, in whom the QT interval is prolonged, as well as in those patients with congestive heart failure complicated by impaired renal and hepatic function.

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We are grateful to Drs. R. W. Dhurandhar and T. B. Tri for additional information about their patients.

Addendum

Since this manuscript was submitted for publication, additional causes of Dysopyramide Induced Ventricular Tachycardia have been reported by Tzivoni and coworkers, Arch Int Med, 1981:946–947, and by Wald and coworkers, J Electrocardiol, 1981; 14:301–308.

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Sarcoidosis with Immune Hemolytic Anemia and Thrombocytopenia: Humoral Aberrations Responding to Steroids or Splenectomy

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Abstract

Sarcoidosis is characterized immunologically by the Kveim-Siltzbach reaction, impaired cellular immunity, and reactive humoral immunity. We present a patient with longstanding sarcoidosis who developed antiglobulin (Coombs')–positive hemolytic anemia and platelet antibody–positive thrombocytopenia ("Evans' syndrome"), who responded to steroid therapy. A literature review documented 15 cases of immune hemolytic anemia and 15 cases of immune thrombocytopenia associated with sarcoidosis. Remission followed treatment with steroids and/or splenectomy in 12 of 13 patients with hemolytic anemia and 13 of 13 patients with thrombocytopenia. Five patients initially responding to therapy had recurrent hemolytic anemia, of whom four died. No responding patient with thrombocytopenia relapsed. Two untreated thrombocytopenic patients died of hemorrhage. The association of sarcoidosis with these autoantibody mediated hematologic disorders appears to reflect aberrant humoral immunity. Prompt institution of therapy and careful follow-up of these patients is essential.

Sarcoidosis is a granulomatous disease of unknown etiology demonstrating multiple immunologic abnormalities. A reliable diagnostic test for sarcoidosis, the Kveim-Siltzbach skin reaction, is thought to have an immunologic basis. Cellular immunity is depressed in sarcoidosis, as indicated by cutaneous anergy, poor lymphocyte mitogen response and reduced T cell population. Heightened antibody titers to viral antigens, increased numbers of B cells, and circulating immune complexes and rheumatoid factor suggest aberrant humoral immunity (1, 2).

Hematologic manifestations of sarcoidosis are varied (3), and include a number of reports of immune hemolytic anemia (4) and immune thrombocytopenia (5). Semple (6) has reported in the British literature a patient with immune hemolytic anemia and thrombocytopenia, "Evans' syndrome" (7), who was later found to have sarcoidosis.

We present a woman with longstanding sarcoidosis who developed Evans' syndrome with coexistent positive antiglobulin (Coombs') test and platelet antibodies.

Case Report

A 56-year-old black woman with an 18-year history of sarcoidosis was admitted to The Mount Sinai Medical Center with five days of gingival bleeding. There had been no previous signs or symptoms of bleeding. The diagnosis of sarcoidosis had been based upon cervical and bilateral hilar adenopathy and confirmed by cervical node biopsy and positive Kveim reaction. The blood count six weeks prior to admission showed a hematocrit of 39.1%, hemoglobin of 12.8 g/dl, and a platelet count of 210,000/mm^3. Physical examination revealed erythematous confluent papules which rimmed both nares and both eyes. Multiple petechiae were found on the hard palate. No purpura was present. There was no hepatosplenomegaly. The rectal examination revealed blood streaking on normal stools. Hematocrit was 41.3%, hemoglobin was 13.2 g/dl, a platelet count was 18,000/mm^3, and white count was 8,400/mm^3.

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Polymorphonuclear leukocytes were 66%, bands, 4%, lymphocytes 24%, monocytes 3%, eosinophils 2%, basophils 1%. Prothrombin time was 12.2 over control of 10.9 seconds. Partial thromboplastin time was 36 seconds with control 36. Fibrinogen was 365.mg/dl. Reticulocyte count was 1.0%. Peripheral smear was without fragmented cells. Megathrombocytes were present. Fibrin split products were absent. Sedimentation rate was 88 mm/hr. Chest x-ray revealed right hilar prominence. Urinalysis showed four to five red blood cells per high power field. Bone marrow examination revealed a normocellular marrow with increased numbers of megakaryocytes. Erythroid and myeloid series showed normal differentiation. The patient was placed on prednisone 60 mg po daily. Three days after admission, the patient was noted to be icteric. Total bilirubin was 4.3 mg/dl, lactate dehydrogenase (LDH) 653 mU/ml (normal less than 220 mU/ml), hematocrit 35.8%, platelet count 27,000/mm^3 (Figure 1). The direct antiglobulin (Coombs') test was positive for IgG, IgM, C3 and C4. The serum haptoglobin was 5 mg/dl. Prednisone was increased to 100 mg daily. Hematocrit fell initially to 28.0% and then stabilized, as the reticulocyte count rose to 8.3%.

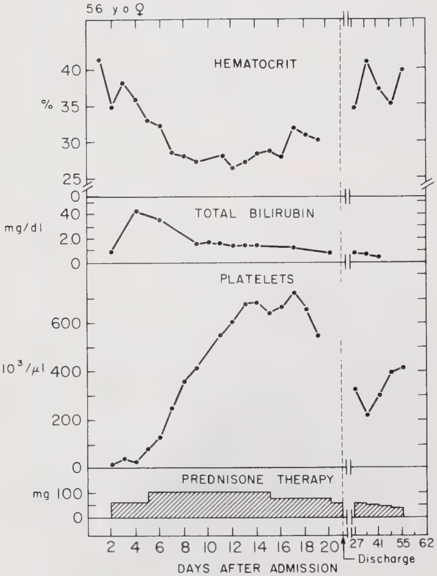

FIG. 1

With continued steroid treatment, the platelet count rose rapidly to normal, without further bleeding. The bilirubin and LDH normalized, and the hematocrit slowly increased. Cold agglutinin titers, Monospot test and heterophile, antinuclear antibody and latex fixation were all negative. Serum protein electrophoresis and immunoelectrophoresis were normal. A repeat Coombs' test on day 14 was negative. Platelet antibodies determined by the platelet factor 3 immunoinjury test (9) through the courtesy of Dr. Margaret Karpatkin were present in a titer of 1:32 on day 10.

Prednisone was tapered slowly and discontinued at the end of six months. The patient has remained hematologically stable.

Materials and Methods

A MEDLARS multilanguage computer search from 1966 through the present was obtained to find all reports of hemolytic anemia and/or thrombocytopenia in sarcoidosis. Earlier references were gleaned from published reviews (3–5).

Case reports were examined and included for analysis if they met the following criteria: 1) Diagnosis of sarcoidosis required histologic evidence or a positive Kveim test (8); 2) Diagnosis of immune thrombocytopenia was accepted when thrombocytopenia was present without pancytopenia, massive splenomegaly, or evidence of disseminated intravascular coagulation, and when no drug reaction or other disease process could be implicated; 3) Diagnosis of immune hemolytic anemia was made when a fall in hematocrit or hemoglobin was accompanied by reticulocytosis and hyperbilirubinemia or icterus in the absence of an indictable drug or disease process.

Discussion

Common hematologic aberrations in sarcoidosis include mild anemia, leukopenia and eosinophilia. Splenomegaly occurs in 6% to 10% of patients (10, 11), and may cause pancytopenia through sequestration of blood elements.

We found the separate occurrence of immune hemolytic anemia and immune thrombocytopenia to be well documented in patients with sarcoidosis (Tables I, II).

Including our patient, fifteen cases of sarcoidosis and immune hemolytic anemia were found (Table I). Patients were between 6 months and 56 years of age. There was no sexual or racial predominance. The Coombs' test was positive in

TABLE I

Immune Hemolytic Anemia in Sarcoidosis

Patient	(Ref)	HGB g/dl[a]	HCT %	WBC 10³/mm³	PLT 10³/mm³	SPLEEN PALPABLE	TISSUE EVIDENCE OF SARCOIDOSIS	COOMBS' TEST
46 F W	(12)	"41%"			480	–	N[c], bone marrow	
						(485g)[b]		
6 mos F B	(13)	"38%"		23.0	130	+	N	
		"43%"		6.6	270	+		
45 F B	(3)	5.2			274	+	N,S,L,	
		7.0		3.8		(500g)		
34 M B	(14)	6.1		6.8	204	(450g)	N,S	–
23 F	(15)	"42%"		9.8	Nl[e]	f	N,S, lacrimal gland	+
		"32%"		10.7	Nl			+
52 M	(16)	7.7		4.8	Nl	–	N	+
55 F	(17)	"60%"		7.7	Nl	+	N, lung	+
		"39%"		18.0	Nl	(900g)		
31 M	(18)	"76%"		4.1	Nl	+	N,S	–
						(430g)		
32 F	(19)	6.0		12.1	414	+	N,S	
						(530g)		
29 M W	(20)		9.5	11.3	Nl	+	N	–
						(1200g)		
35 M	(21)	7.8		4.5	180	+	N,S	+
						(630g)		
41 F	(22)	10.7		7.6		–	Kv, bronchial mucosa	+
53 M	(23)	8.5		2.1	55	+	S,L	–
		7.6		26.0		(1250g)		+
25 M	(16)	10.9			Nl	–	N, Kv, soft tissue mass	+
56 F B	g	9.3	28.0	12.6	27	–	N,Kv	+

TABLE I CONT.

Immune Hemolytic Anemia in Sarcoidosis

Patient	(Ref)	EVIDENCE RETICS %	HEMOLYSIS BILI mg/dl	THERAPY	OUTCOME
46 F W	(12)	44.0	d	Splenectomy	Remission; relapse in 2 months; death
6 mos F B	(13)	8.2	d	Nonspecific	Remission; relapse at 8 yr; no f/u
		15.0			
45 F B	(3)	22.0	1.0	Splenectomy	Remission; relapse in 8 months; no f/u
		23.6			
34 M B	(14)	20.0	2.3	Steroids & Splenectomy	Remission; steroid dependence
23 F	(15)	15.0	3.2	Steroids	Remission; relapse in 5 months; death 8 months later
		23.6	6.4	Steroids	
52 M	(16)		4.0	Steroids	Remission
55 F	(17)	21.2	d	Steroids	Remission; relapse in "months" CVA, death
		28.5			
31 M	(18)	2.3	1.9	Splenectomy	Remission
32 F	(19)	29.8	2.9	Splenectomy	Remission
29 M W	(20)	8.0	1.0	Steroids & Splenectomy	No response; no f/u
35 M	(21)	55.4	4.7	Splenectomy	Remission
41 F	(22)	7.6	1.8	Azathioprine Chlorambucil	No response; cold agglutinin disease
53 M	(23)		2.2	Splenectomy	Remission; relapse in 11 months; death
		12.0	5.2		
25 M	(6)	19	d	Steroids	Remission
56 F B	g	8.3	4.3	Steroids	Remission

a. Unless units specified as % instead.
b. Spleen weight at splenectomy or autopsy.
c. Node (N), Spleen (S), Kveim (Kv), Liver (L).
d. Jaundiced.
e. Normal on peripheral blood smear.
f. Splenectomy done for hypersplenism six months prior to first episode hemolysis.
g. Our patient.

TABLE II

Immune Thrombocytopenia in Sarcoidosis

PATIENT	(REF)	HGB g/dl[a]	HCT %	WBC 10^3/mm^3	PLT	SPLEEN PALPABLE	TISSUE EVIDENCE OF SARCOIDOSIS	PLATELET ANTIBODIES	TREATMENT	OUTCOME
27 F	(24)	13.5		11.8	80	+ (275g)[b]	S[c]		Splenectomy	Remission
37 M W	(3)	13.1		8.8	36	+ (680g)	S		Splenectomy	Remission
55 M W	(25)	14		5.5	d	(210g)	S		Splenectomy	Remission
16 F W	(26)	6.0		5.4	15	+	S		Splenectomy	Remission
15 F W	(27)	"65%"		6.5	d	+ (210g)	N, S, L, Kidney		None	Intracranial bleed; death
16 F	(28)	"90%"		9.5	d	+ (95g)	S		Steroids & Splenectomy	Remission
30 F	(29)	10.0		5.0	10	+ (280g)	N, S, Lung, Thyroid		None	GI bleed; death
29 M B	(30)	13		9.6	9.6	–	N		Steriods	Remission
13 M B	(5)	9.8		10.1	7	+	N, Kv		Steroids	Remission
14 M B	(5)		32	10.2	d	+	L		Steroids	Remission
63 F W	(31)	12.3		3.2	26	(258g)	S, Kv, Skin	+ 1:4	Steroids & Splenectomy	Remission
17 M	(32)	15		4.6	41		N		Steroids	Remission
25 M	(6)	17.4		8.5	50	–	N, Kv, soft tissue mass	Weakly +	Steroids	Remission
24 F	(33)		35	4.7	6	–	N		Steroids	Remission
56 F B	e	13.2	41.3	8.5	18	–	N, Kv	+ 1:32	Steroids	Remission

a. Unless units specified as % instead.

b. Spleen weight at splenectomy or autopsy.

c. Node (N), Spleen (S), Kveim (Kv), Liver (L).

d. Markedly decreased on peripheral blood smear.

e. Our patient.

eight patients, negative in three patients, and not reported in four. Splenomegaly was unusually common; eight patients had palpable spleens, two of which were massively enlarged at splenectomy (20, 23).

Three patients with hemolytic anemia responded to steroids, three responded to splenectomy, and one responded to a combination of steroids and splenectomy, all with lasting remissions (Table III). Each of five patients had two distinct episodes of hemolysis, relapsing after initial response to therapy. Two relapsed and died after first remitting on steroids. Of three who had recurrent hemolysis after early response to splenectomy, two died. One patient, a 6-month-old girl, remitted without therapy, then hemolyzed again when 8-years old. One patient failed to make even a transient response to treatment, failing to both steroids and splenectomy. Another did not benefit from azathioprine and chlorambucil therapy.

Fifteen cases of sarcoidosis and immune thrombocytopenia fulfilled diagnostic criteria (Table II). Patients ranged from 13 to 63 years of age. There was no sex or race predominance. In all cases, platelet counts were low, although quantitation was not provided in some reports. The spleen tip was palpable in eight cases, but none had pancytopenia. The platelet agglutination test was positive in low titer at the time of thrombocytopenia in one case (31). Platelet antibodies were "weakly positive" 2½ years after an episode

TABLE III

Results of Treatment of Immune Hemolytic Anemia and Thrombocytopenia in Sarcoidosis

Treatment	Immune Hemolytic Anemia	Immune Thrombocytopenia
Steroids		
Lasting remission	3	7
Remission, then relapse	2 (2)+	0
Failure	0	0
Splenectomy		
Lasting remission	3	4
Remission, then relapse	3 (2)	0
Failure	0	0
Steroids and Splenectomy		
Lasting remission	1	2
Failure	1	0
No Therapy		
Spontaneous remission, then relapse	1	0
Died untreated	0	2 (2)
Total Patients	14* (4)	15 (2)

+ Numbers in parenthesis indicate patients who died.

* One patient with immune hemolytic anemia made no response to azathioprine and chlorambucil therapy.

of thrombocytopenia in another patient (6), who appears in both tables and is the other reported case of Evans' syndrome in sarcoidosis.

Seven patients responded to steroids alone, four to splenectomy alone, and two to a combination of steroids and splenectomy (Table III). In these thirteen patients the thrombocytopenia remitted, and there were no reported recurrences. Two patients died prior to treatment, one of intracranial hemorrhage and one of gastrointestinal bleeding.

Initial therapeutic response to steroids and/or splenectomy was excellent in both groups (Table III). Hemolysis ceased in 12 of 13 treated patients with immune hemolytic anemia, and platelets rose to normal levels in all 13 patients treated for immune thrombocytopenia. Five patients had recurrent hemolysis, and four died. Particular caution must be exercised in the follow-up of such sarcoidosis patients with immune hemolytic anemia in remission; they may require prolonged steroid therapy and frequent hematologic surveillance. Patients with immune thrombocytopenia fared better, with no relapses reported once therapy had been effective. However, the two thrombocytopenic patients who died before treatment serve to emphasize the importance of prompt institution of either steroid therapy or splenectomy in these patients with sarcoidosis.

Not included in this series of patients are five cases of reported sarcoidosis among 110 with "secondary thrombocytopenic purpura" studied by Doan et al (34). Histologic evidence of sarcoidosis was not presented. Our patient is the third to have platelet antibodies in association with sarcoidosis. Pillay has presented a patient with acute erythema nodosum and bilateral hilar lymphadenopathy but without histologic evidence of sarcoidosis who developed profound thrombocytopenia associated with a positive indirect platelet antiglobulin test (35). The thrombocytopenia remitted with steroid therapy.

The subset of patients with sarcoidosis presenting with acute erythema nodosum and bilateral hilar adenopathy is of particular immunologic interest in that they may have circulating immune complexes (36). In a recent study, 12 of 26 patients with sarcoidosis of less than one-year duration had immune complexes demonstrated by an indirect immunofluorescence assay using the Raji cell line (37). Six sarcoidosis patients were reported by Hedfors and Norberg to have positive direct platelet aggregation tests for circulating immune complexes (38). It is conceivable that the immune complexes may act clinically as antiplatelet antibodies.

The association of immune hematologic disorders with sarcoidosis may reflect general antibody stimulation, a common immunologic manifestation of sarcoidosis (1). Serologic studies in sarcoidosis have revealed elevated circulating immunoglobulin levels (39), increased antibody titers to common viruses (40, 41), and increased antibody response to mismatched blood (42). Rheumatoid factor is present in up to 47% of cases of sarcoidosis (43, 44). Immunoglobulin-bearing B lymphocytes are significantly increased in patients with sarcoidosis (45, 46). Autoantibodies have not generally been found with unusual frequence in sarcoidosis (1, 47, 48).

Immunologic processes are postulated to play a role in the pathogenesis of sarcoidosis (49). The Kveim reaction is believed to have an immunologic basis. Cellular immunity is impaired in sarcoidosis, as indicated by cutaneous anergy, poor lymphocyte response to mitogens, and reduced T cell numbers (1, 2). An appealing hypothesis is that autoantibodies to suppressor T cells cause enhanced activity of B cells in sarcoidosis (49). Aberrant humoral immunity is apparent in the cases of immune hemolytic anemia and immune thrombocytopenia collected here. This may be especially noted in the fact that the two cases of Evans' Syndrome, ours and Semple's, exhibit positive antibodies to red cells (positive Coombs') and antiplatelet antibodies.

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Intraoperative Diagnosis of Bronchoesophageal and Malignant Gastrocolic Fistulae: A Case Report

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Abstract

The following case report represents the unusual coexistence of bronchoesophageal and gastrocolic fistulas in a 74-year-old man. While the etiology of the former fistulization was not confirmed histologically, the case is important because of its presentation and because a diagnosis was made based upon intraoperative events during the administration of anesthesia and assisted ventilation. A discussion of clinical diagnosis and a brief review of the possible etiologies follows.

Case Report

A 74-year-old man was admitted to the City Hospital Center, Elmhurst, on June 16, 1979, with a three-day history of confusion, abdominal pain, melena and hematemesis and a recent history of cough. He was a chronic alcohol abuser and had a 60-pack year smoking history. No chest pain or abdominal pain. No history of tuberculosis.

Physical examination revealed a Cachectic confused man in moderate respiratory distress. His pulse was 85/minute, blood pressure was 11/70 toor with orthostatic changes. Respiration was 20/minute and a rectal temperature of 98°F. Sclerae were icteric. Diminished breath sounds at left base with few scattered rhonchi. Regular sinus rhythm with occasional ventricular premature contractions documented by ECG. No murmurs or abnormal sounds. A tender flat mass was palpable in the upper left mid epigastrium. No ascites. Skin showed marked palmer erytheme and few spider angiomata. Anal sphincter was lax and feces were positive occult blood.

Past medical history was remarkable for cholecystectomy (1960), vocal cord stripping (1965), excision of perianal fistula (1970), and retropubic prostatectomy performed in November, 1979, during which endotracheal intubation and anesthesia were administered uneventfully.

Chemistries on admission revealed a serum sodium of 127 mEq/liter; potassium, 4.9 mEq/liter; urea nitrogen, 49 mg/dL; chloride, 90 mEq/liter; creatinine, 0.9 mg/dL; bicarbonate, 26 mEq/liter; and glucose, 325 mg/dL. Serum amylase was 65 units and the prothrombin time was 15.1 seconds as compared to the 11.2 second control. Initial total serum bilirubin was 1.4 mg% with a repeat determination of 2.2 mg%. Laboratory data showed a hypochromic, microcytic anemia with a hemoglobin of 6.5 g/dL and a hematocrit of 20.7% with a total white blood cell count of 36,500/cu mm with 89% neutrophils, 8% band forms, 2% lymphocytes and increased platelets. The patient was transfused with three units of packed red blood cells with a resultant hematocrit of 28%. A suboptimal barium upper gastrointestinal tract series obtained the day after admission revealed a Zenker's diverticulum. On June 23rd, esophagogastroduodenoscopy was performed and demonstrated a superficial ulcer on the posterior wall of the body of the stomach. A biopsy was taken which subsequently proved to be gastric mucosa with chronic inflammatory exudate. The biopsy site bled after the procedure requiring the transfusion of three additional units of packed cells after which the patient's status stabilized. Ultrasound examination of the abdomen revealed a cystic mass over the epigastrium and an echo-free region in

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the left lobe of the liver (Fig. 1). A repeat barium esophagogram again showed the Zenker's diverticulum and a possible mass effect at the lower esophagus (Fig. 2).

Two days later, the patient became febrile to 101.4°F and repeat blood studies revealed a total white blood cell count of 20,000/cu mm with 65% polymorphs and 21% band forms. Multiple blood samples, sputum, and urine cultures failed to provide a causitive agent. Liver function studies showed the patient to be hypoalbuminemic, total bilirubin, serum alkaline phosphatase, and lactic dehydrogenase were moderately elevated. Chest radiograph revealed findings consistent with longstanding chronic obstructive pulmonary disease but without obvious infiltrates. Repeat chest x-ray taken at the time of the temperature spike showed a small left lower lobe infiltrate (Fig. 3). Liver scan demonstrated nonspecific, diffusely decreased uptake consistent with parenchymal involvement probably secondary to alcoholic liver disease. Treatment with intravenous ampicillin was initiated but the patient continued to spike temperatures. Ampicillin was later discontinued and fever remitted spontaneously although the elevated white count persisted. Gallium scan performed on July 10th showed a well-circumscribed area of increased uptake in the midepigastrium just to the left of the midline. The patient's status continued to deteriorate with significant weight loss. A provisional diagnosis of intra-abdominal abscess versus carcinoma was proposed and a surgical insulation was obtained.

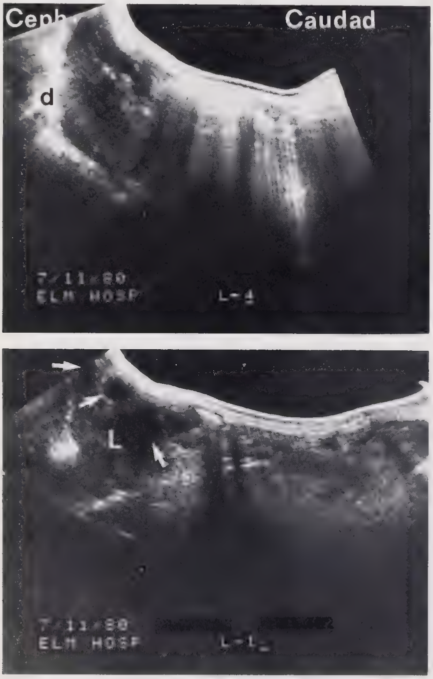

Fig. 1

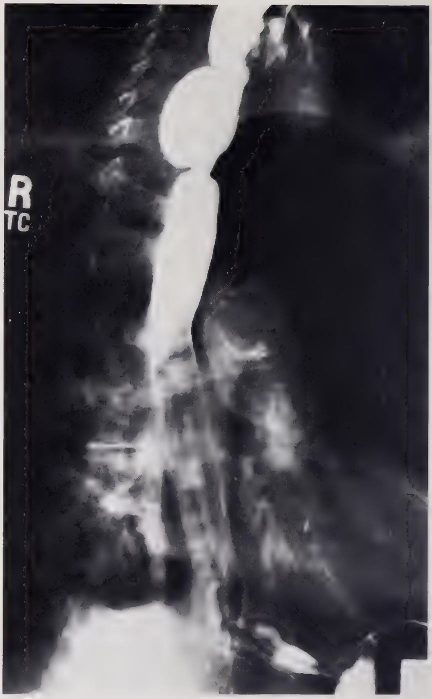

Fig. 2

Exploratory laparotomy was performed on July 25, 1980. After rapid induction with sodium pentothal and succinylcholine, the endotracheal tube was inserted after direct visualization of the vocal cords. Upon inflation of the cuff and subsequent ventilation, the abdomen immediately distended. The patient's trachea was extubated and reintubated, again with direct visualization of the cords, but the same phenomenon recurred. When the cuff of the endotracheal tube was deflated, the abdomen could be flattened by compression, with

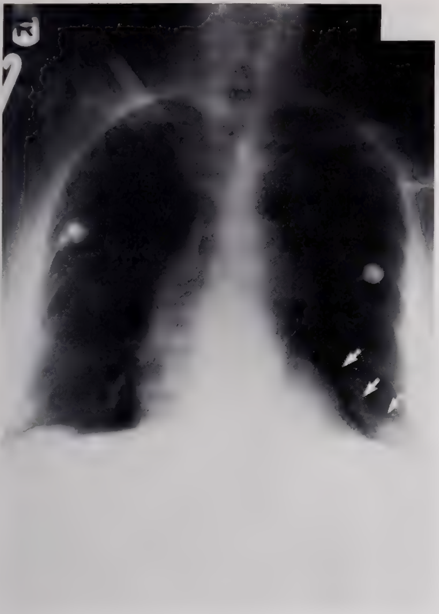

FIG. 3

air heard leaking around the tube. The patient's trachea was extubated and intubated a third time, but the tube was intentionally inserted into the right main bronchus so that breath sounds were only heard on the right side in order to ascertain that the endotracheal tube had indeed traversed the trachea. The tube was then gradually withdrawn until breath sounds were present bilaterally and equally. The cuff was inflated and the abdomen again began to distend increasingly with each ventilation. The probability of a tracheoesophageal or bronchoesophageal fistula was considered at that time. Since the procedure was an emergency, it was decided to proceed with anesthesia. The endotracheal tube was left in place with the cuff deflated. Anesthesia was maintained with a high flow mixture consisting of nitrous oxide and oxygen, 5L:5L, with 2.5% enflurane.

The abdomen was then opened and a huge tumor mass was palpated in the upper abdomen. The tumor appeared to originate from the body of the pancreas with extensive invasion of the stomach, and extended upward to the mediastinum. The transverse colon adhered to the stomach. The cuff of the endotracheal tube was inflated, positive-pressure ventilation was performed, and the transverse colon distended. When the cuff was deflated, the colon was easily deflated by manual compression. Repeating the procedure yielded the same result.

In view of the above findings, it was concluded that there must have been a left-sided bronchoesophageal fistula and a gastrocolic fistula present concomittantly. It could thus be explained how air could pass from the trachea (and bronchus) into the esophagus, and subsequently into the stomach and, finally, via the gastrocolic fistula into the transverse colon. The operative procedure lasted twenty minutes. Only a tissue biopsy was performed which revealed poorly differentiated, infiltrating adenocarcinoma. The patient awakened immediately after the procedure, was extubated, and after one hour was transferred to his ward from the recovery room. Some thirty hours later the patient expired. Permission for autopsy was refused.

Discussion

Anomalous communications between the esophagus and respiratory tree fall into the following main categories as outlined by Smith (Table I) (1).

Tracheoesophageal fistulas are usually congenital in origin, recognized early, and operated upon in the neonatal period. Bronchoesophageal fistulas, while only half as common as the tracheoesophageal variety, are more insidious in onset. The usual presentation consists of recurrent pneumonia and chronic pulmonary sepsis. The patients complain of chronic, productive cough, hemoptysis, food in the sputum, vomiting,

TABLE I

*Anomalous Esophagorespiratory Communications**

I. *Benign:*
  a) Congenital: (i) infants, with or without esophageal atresia
    (ii) adults, without esophageal atresia
  b) Acquired: (i) traumatic
    (ii) inflammatory, either tuberculous or as a result of mediastinitis

II. *Malignant Invasion* secondary to:
  a) Bronchogenic carcinoma
  b) Esophageal carcinoma
  c) Primary or secondary hilar node metastases

* adapted from Smith (1)

and prolonged bouts of coughing on swallowing liquids and occasionally solid foods.

In a review of 23 cases of congenital bronchoesophageal fistulas, Braimbridge and Keith described four different types (Fig. 4) (2). Type one is associated with a wide-necked congenital diverticulum of the esophagus that perforates into an airway following an inflammatory process. It may, at times, be difficult to differentiate this diverticulum from the traction type. Type two is a simple tract joining the esophagus to a lobar or segmental bronchus. Type three is a fistulous tract with a cyst interposed between the two hollow viscera. Type four is a fistula entering the bronchus of a sequestered pulmonary segment which receives an independent blood supply directly from the aorta.

How these congenital fistulas can persist into adult life without persistent symptomatology has been the topic of much discussion in the literature. The late appearance of symptoms and diagnosis has been explained in various ways. The presence of a membrane that subsequently ruptures allowing passage of ingested material through the now free communication (3), the presence of a flap-like valve of esophageal mucosa that subsequently becomes incompetent (4), and the frequently demonstrated, upwardly oblique nature of the tract which may close during swallowing (thus preventing reflux under ordinary circumstances (5), have all been proposed. However, a recently reported case (6) of a 58-year-old man found no evidence that any of these mechanisms were operative.

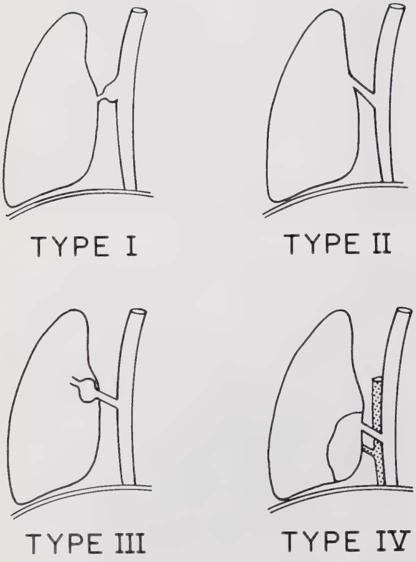

Fig. 4

Up to the time of their case report and review of the literature in 1978 (which included the large study of Blackburn and Amoury (7)), Chu and Mullen had found only 69 cases of bronchoesophageal fistula in the adult (6). They reported that the age at time of diagnosis in this series of cases varied from the late teens to the seventh decade of life. It is important to realize that the congenital nature of these fistulas has been presumed on the basis of histologic verification of a definite mucosa (squamous, columnar, and transitional types have all been described (1)), muscularis mucosa, and the absence of neoplastic or inflammatory changes or adherent lymph nodes subsequent to fistulectomy (8). Finally, Ramanathan et al noted that in the great majority of reported cases of bronchoesophageal fistula, the fistulous tract took origin from the distal third of the esophagus (9).

In a large series reviewing 500 cases of esophageal-pulmonary communications from all causes, malignant neoplasms, trauma, and infection accounted for 72% of the cases (10). Other much less common causes of esophageal-pulmonary communication have been reported. They include: esophageal diverticula (11), necrotizing vasculitis (11), and the persistent congenital fistulas formerly mentioned (1, 2, 4–7, 9, 12).

In this case report, we did not have confirmatory histologic evidence of the etiology of the fistula described since the operative procedure was abbreviated because of the difficulty with ventilation and the nature of the lesion. In addition, permission for autopsy was not granted. It may be postulated, based on history and the results of diagnostic studies, the probable origin of the lesions encountered. Firstly, it is highly unlikely although possible that the patient's bronchoesophageal fistula was congenital in origin since he had undergone a major operative procedure requiring endotracheal intubation and general anesthesia less than one year prior to this admission. Since the intraoperative intubation and ventilation of the right main bronchus failed to result in inflation of the stomach or colon, we assume the fistula was localized to the trachea at or above the carina or, more likely, to one of the segmental branches of the left main bronchus supplying the left lower lobe. While the diagnosis is usually made by barium swallow in up to 65% of cases (2), upper gastrointestinal series did not reveal a fistulous tract. As was previously mentioned, the films were unsatisfactory and other authors have emphasized the importance of using a dilute barium solution and placing the patient in the position in which he finds his symptoms most marked as the tract may otherwise be missed (13). Upper gastrointestinal endoscopy, as has been frequently reported, failed to identify the orifice of the fistulous tract (1, 2, 6, 9, 14). Bronchoscopy has also infrequently demonstrated the orifices of fistulas, usually being successful only when exact sites are known (2). In spite of extensive investigation, the diagnosis of bronchoesophageal fistula may only be made at surgery in up to 35% of cases (2).

Secondly, the etiology of the bronchoesophageal fistula in this case may be secondary to malignant infiltration of the distal third of the esophagus by the pancreatic adenocarcinoma seen at laparotomy to be extending upward to the mediastinum or less likely to infiltrating periaortic or paratracheal neoplastic lymph nodes. In addition, a recently reported case of Boerhaave's syndrome complicated by spontaneous formation of an esophageal-bronchial fistula bears marked resemblance to portions of this case and should be considered (14). Although the syndrome is almost invariably fatal if not treated as a surgical emergency and classically presents with the acute onset of tachypnea, abdominal pain, rigidity, and subcutaneous emphysema rapidly followed by shock and sepsis, the case referred to above described a six-week chronic indolent course tolerated because the mediastinal contamination following the initial esophageal tear was well-contained and allowed sufficient time for the spontaneous formation of the fistula (14).

Thirdly, since malignant infiltration of the stomach and duodenum is reported in up to 20% of cases of pancreatic carcinoma, it is likely that the gastrocolic fistula discovered at laparotomy had such an origin. It is unusual, however, that both the posterior and anterior walls of the stomach were involved. Most probably carcinomatous metastases seeding the serosal surface of the transverse colon were responsible for its adherence to the anterior stomach wall and subsequent fistulization.

Finally, although no evidence for its existence was found, a gastrobronchial fistula, whose presence concomitantly with a gastrocolic fistula would lead to similar intraoperative events to those encountered in this case report, is mentioned as a possibility only for completeness. While most often a complication of subphrenic abscess, gastrobronchial fistula may also be caused by direct trauma to the chest and abdomen, infiltrating neoplasm, and perforation of the stomach while incarcerated in a diaphragmatic hernia (15−17). A recent report by Quasha and Pairolero at the Mayo Clinic described the intraoperative diagnosis of gastrobronchial fistula in a 33-year-old alcoholic man undergoing repair of a large left diaphragmatic hernia because of persistent gastroesophageal reflux (18). The intraoperative occurrence of a sudden loss of tidal volume with increasing gastric distention which fluctuated with ventilation following endotracheal intubation and ventilation closely mimicked our case. The etiology of the gastrobronchial fistula was secondary to erosion of a gastric ulcer into the mediastinum and an adjacent mainstem bronchus (18).

While it is beyond the scope of this report to detail the treatment of broncho-esophageal fistula, most authors have described successful closure of the fistula and removal of permanently damaged segments of the lung as resulting in permanent cure when not associated with carcinoma.

Summary

This paper has briefly dealt with the intraoperative diagnosis of bronchoesophageal and gastrocolic fistulas. Assuming correct and accurate endotracheal intubation, and barring failure of the mechanical ventilator or a large leak in the anesthesia circuit or endotracheal tube, the sudden loss of tidal volume encountered could only have been accounted for by a fistula in the tracheobronchial tree. The etiologies of such fistulas were mentioned with emphasis on the most frequent types encountered. A discussion dealing with the proposed mechanism of fistulization between the respiratory and digestive systems is described.

Acknowledgments

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Persistent Renal Failure Following Administration of Naproxen

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Abstract

Oliguric acute renal failure developed in a patient during the administration of naproxen, a nonsteroidal, anti-inflammatory agent. Percutaneous renal biopsy revealed interstitial nephropathy. The renal failure, managed with dialysis for forty days, failed to remit either spontaneously or following a therapeutic trial of corticosteroids.

Introduction

Oliguric acute renal failure developed in a patient during the administration of naproxen, a nonsteroidal, anti-inflammatory agent. Percutaneous renal biopsy revealed an interstitial nephropathy. The renal failure, managed with dialysis for forty days, failed to remit either spontaneously or following a therapeutic trial of corticosteroids. The clinical and pathological features of this case are described.

Case Report

An 85-year-old woman was admitted to the hospital with melena and renal failure.

The patient had a 25-year history of mild hypertension, treated with propranolol, 20 mg, four times daily. She received digoxin, 0.125 mg daily for four years following hospitalization for atrial fibrillation. Five weeks prior to admission her physician prescribed naproxen, 250 mg, twice daily for shoulder and back pain. The patient was admitted to the hospital after noting three days of tarry stools.

On admission, the patient was in no acute distress. The blood pressure was 130/80 mmHg, without orthostatic change. Mild epigastric pain, pedal edema and melanotic stools were noted on examination. Laboratory studies revealed a hematocrit of 33%, blood urea nitrogen of 120 mg/dl, serum creatinine of 5.8 mg/dl, serum sodium of 132 mEq/l, serum potassium of 7.0 mEq/l, serum chloride of 118 mEq/l and serum bicarbonate of 18 mEq/l. Urinalysis showed 1+ protein and the sediment contained two white blood cells per high power field. There were 120 mgs of protein in a 24 hour specimen. Serum complement and serum protein electrophoresis were normal. The serum was negative for anti-nuclear antibodies. Four months prior to admission, the hematocrit was 43%, blood urea nitrogen 17 mg/dl and serum creatinine 1.1 mg/dl.

Urine volume was less than 15 ml per hour. Peritoneal dialysis was initiated for management of renal failure and hyperkalemia. During dialysis, blood transfusions were given. Esophagogastroduodenoscopy was then performed and revealed two large duodenal ulcers without active bleeding. Renal ultrasound and retrograde pyelogram demonstrated normal sized kidneys and the absence of urinary tract obstruction.

She developed pleural effusions, nausea, anorexia and weight loss. Renal failure and severe oliguria persisted, necessitating repeated courses of peritoneal dialysis. Percutaneous renal biopsy was performed on the thirteenth hospital day. Thereafter, she received prednisone, 60 mg per day for ten days, and courses of peritoneal dialysis were resumed. There was no apparent improvement in renal function. In the fifth week of hospitalization, the patient and her family refused any further treatment, and she died in renal failure forty days after admission. Permission for postmortem examination was denied.

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Histopathology

On light microscopy, the percutaneous kidney biopsy revealed the glomerular architecture to be well preserved with only slight wrinkling of the capillary walls. The tubules showed occasional thickening of basement membranes and scattered hyaline cysts. The changes in the interstitium were striking. There was marked intertubular edema and moderate leukocytic infiltration of polymorphonuclear neutrophils, lymphocytes and eosinophils. Electron microscopy revealed minimal glomerular changes with occasional foot process effacement and microvilli in the urinary space. The interstitial tissue was edematous and contained may lymphocytes and polymorphonuclear leukocytes. Immunofluorescent microscopy showed no deposits of immunoglobulins, complement or fibrinogen in the interstitium, tubular walls or blood vessels. There were no glomeruli present for immunologic study.

Discussion

The patient presented here developed oliguric acute renal failure which persisted for forty days. Renal biopsy revealed interstitial leukocytic infiltration and edema, suggesting that acute interstitial nephritis was the likely pathologic lesion underlying the renal failure. Gastrointestinal bleeding may also be incriminated as a cause for acute renal failure. However, findings of moderate anemia without active bleeding or hypotension make vasomotor nephropathy unlikely. Furthermore, the pathologic finding of marked interstitial changes with preservation of tubular architecture favors a diagnosis of drug-related nephrotoxicity.

Renal failure occurred in this patient during administration of naproxen, a nonsteroidal anti-inflammatory agent. Two patients have recently been reported implicating naproxen as a cause for decreased renal function; one of the patients manifested nephrotic syndrome (Table I) (1, 2). Kidney biopsy revealed acute interstitial nephritis on light microscopy in both patients. Return of kidney function occurred after withdrawal of the drug. Our patient represents the first report, to our knowledge, of persistent renal failure despite discontinuation of naproxen. In addition, unlike previous reports, other potentially nephrotoxic agents were not given.

The incidence of kidney toxicity following naproxen therapy is apparently uncommon. The

TABLE I
Interstitial Nephritis During Naproxen Administration

Age and Sex:	16-year old male	61-year old male	85-year-old female
Previous Kidney Function:			
Urea Nitrogen	NA(1)	NA	17 mg/dl
Serum Creatinine	NA	NA	1.1 mg/dl
Diseases:	Rheumatoid Arthritis & Hodgkin's Disease	Knee pain	Shoulder pain
Naproxen Dosage/day:	500 mg.	500 mg.	500 mg.
Time	4 months	1 year	5 weeks
Other Medications:	Aspirin 2.4 grams/day for 4 months (received aspirin & gold for 2 years prior)	Ser-Ap-Es(2) & chlordiazepoxide for many years	Propranolol & digoxin for many years
Renal Insufficiency Peak Values:			
Urea Nitrogen	67 mg/dl	NA	Required dialysis
Serum Creatinine	4.8 mg/dl	6.1 mg/dl	
24 hour protein	1+	16.8 gm	120 mg.
Pathology:			
Light microscopy	Mononuclear interstitial infiltrate Occasional focal glomerular hypercellularity, increase in mesangial matrix	Interstitial edema & cellular infiltration	Interstitial edema & cellular infiltration
Electron microscopy		Foot process effacement	Foot process effacement
Recovery Values:			
Urea Nitrogen	NA	NA	Patient died after withdrawal of dialysis 40 days after admission
Serum Creatinine	1.1 mg/dl	1.0 mg/dl	
Time	1 week	1 month	
Reference:	(2)	(1)	Present Case

(1) NA - not available; (2) Ser-Ap-Es - a combination tablet of reserpine, hydrochlorothiazide and hydralazine.

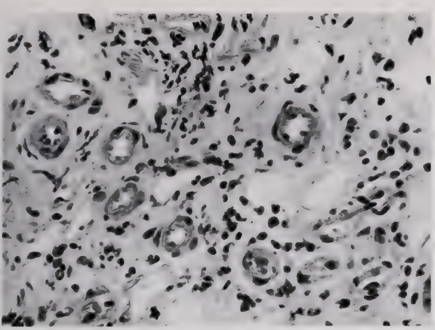

FIG. 1A. Light microscopy of kidney biopsy specimen showing moderate interstitial inflammatory infiltration and marked interstitial edema (hematoxylin and eosin, 350× magnification).

Committee on Safety of Medicines of Great Britain report twenty-six possible cases since introduction of the drug in Great Britain in the early 1970's. (Committe on Safety of Medicines—Personal Communication) Other nonsteroidal anti-inflammatory agents have been implicated in causing a reduction in renal function in association with an interstitial nephritis (3–5). A number of cases of interstitial nephritis, frequently accompanied by nephrotic syndrome, have been recently reported during therapy with fenoprofen, a phenylalkanoic acid similar in structure to naproxen (1, 3, 4).

Interstitial nephritis has complicated the administration of a variety of drugs (6). A number of mechanisms have been proposed to explain the interstitial reaction, including direct cellular toxicity (7), immunologic reaction involving humoral or cellular mechanisms (8, 9), and intrarenal hemodynamic changes (7). The mechanisms underlying the interstitial nephritis associated with the nonsteroidal anti-inflammatory agents remains unclear. The recognition that this group of drugs exerts its anti-inflammatory action through inhibition of prostaglandin synthesis suggests that hemodynamic factors may be, at least in part, responsible for the nephrotoxicity. Considerable evidence has accumulated showing the importance of local hemodynamic effects of intrarenal prostaglandins. In a recent report, reduced renal function, in association with decreased excretion of urinary prostaglandin E-like material, was observed in patients receiving ibuprofen, naproxen and fenprofen (10).

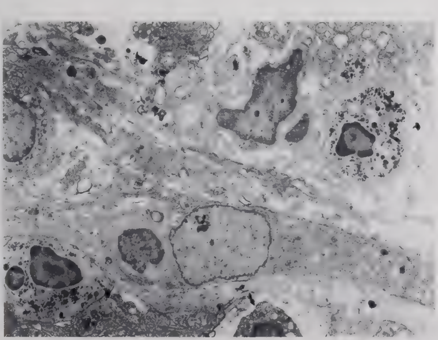

FIG. 1B. Electron microscopy reveals interstitial infiltration of granulocytes, mononuclear cells and renal interstitial cells (uranyl acetate and lead citrate, 4160× magnification).

In summary, a patient is presented in whom persistent renal failure occurred following the administration of naproxen. A spectrum of functional and structural renal abnormalities have been recognized as potential complications of this group of drugs. It would therefore appear prudent to monitor kidney function during the administration of these agents.

Acknowledgments

We are indebted to Drs. H. Gold and J. Graf for referring this patient.

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Dysrhythmia Occurring During Epidural Anesthesia with Bupivacaine

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Abstract

A patient developed atrial fibrillation concurrently with the onset of epidural anesthesia. This dysrhythmia persisted until the termination of anesthesia. Possible mechanisms of production of this dysrhythmia are discussed.

Case Report

The patient was a 77-year-old man scheduled for a left inguinal herniorrhaphy. He had a history of stable angina pectoris and was being treated with propranolol 10 mg tid, po, isosorbide dinitrate 5 mg tid, po, and glyceryl trinitrate 0.4 mg sublingually prn. He also had peripheral vascular disease and a hiatus hernia with reflux. There was no history of cardiac dysrhythmias.

Admission examination showed a small elderly male, height 62 inches, weight 46.4kg. Blood Pressure was 130/90 mmHg, and the pulse rate was 84/min and regular. Pulses in both lower limbs were diminished. A large left inguinal hernia was present which was easily reducible. The remainder of the examination was essentially negative. There was no evidence of congestive cardiac failure.

Laboratory findings were as follows: Hemoglobin/hematocrit 14.49/42.3, WBCS 11.700. Electrolytes: Serum potassium 4.9 mEq/L, sodium 138 mEq/L, chloride 100 mEq/L, bicarbonate 30 mEq/L. The serum glucose level was 78 mg% and BUN 35 mg%. EKG showed an old inferior wall myocardial infarction. Normal sinus rhythm at a rate of 80/min was present, the PR interval was 0.16 seconds and there was no deviation of the electrical axis. Chest x-ray showed increased interstitial markings.

He was premedicated with meperidine 50 mg and diazepam 10 mg im, one hour prior to surgery. He was calm but alert. BP 150/80, pulse rate 100/min and regular. The EKG monitor showed normal sinus rhythm.

The patient was placed in the right lateral position. Following skin sterilization, draping and local infiltration with 1% xylocaine, the epidural space was located at L3–4 with a number 18 Tuohy needle and a loss of resistance technique. A test dose of 3 ml of 0.5% bupivacaine was injected followed after three minutes by 17 ml of 0.5% bupivacaine.

On return to the supine position, blood pressure was 130/80 and pulse rate 100/min. The EKG monitor again showed regular sinus rhythm. A change in rhythm was noted in the EKG monitor some 20 minutes after epidural injection while the anesthesia level was being tested (at T9).

The dysrhythmia was irregular and atrial fibrillation was diagnosed when an electrocardiogram was taken. The ventricular rate increased to 135/min. The BP remained stable 130/80–150/80 mmHg. The patient received propranolol 0.5 + 0.5 mg by slow I.V. injection and 0.25 digoxin I.V. The ventricular rate decreased to 110/min. Blood pressure remained stable 148/78. Arterial blood gas values were pH 7.4, $paCO_2$ 40.1, paO_2 148 mmHg, (on 40% O_2 by face mask) and HCO_3 25 mEq/L.

Surgery lasted one hour and ten minutes. The patient was transferred to the recovery room and placed on an ECG monitor that showed atrial fibrillation with ventricular rate of 120/min, BP 140/80 mmHg.

One and a half hours later (two hours and 50 minutes from the time of injection) when the pa-

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tient no longer had epidural blockade there was abrupt reversion to normal sinus rhythm.

The patient had one further dose of digoxin 0.125 mg I.V. 30 minutes later. He remained in regular sinus rhythm for the remainder of his hospital stay and has evidenced no dysrhythmia at his post-operative visit.

Discussion

The dysrhythmia in this patient is of interest in that the onset of atrial fibrillation occurred with the onset of the epidural block. More importantly, the atrial fibrillation persisted despite treatment during the period of epidural blockade. Reversion to sinus rhythm only occurred when anesthesia had worn off. While electrophysiologic investigation of bupivacaine has not yet received the same attention as has lidocaine, all present evidence indicates bupivacaine has equivalent antidysrhythmic effects to lidocaine in equipotent doses. (1–3). We must, therefore, explain how a dysrhythmia may occur in the presence of an antidysrhythmic drug.

Most dysrhythmias result from disturbances in impulse generation (ectopic) or impulse conduction (re-entrant) or from a combination of both processes (4).

Latent pacemakers may accelerate in frequency or phase 4 depolarization occur in nonpacemaker cells in response to anoxia, stretch, edema or increased sympathetic stimulation (5).

Re-entrant dysrhythmias require an appropriate anatomic pathway, depression in conduction velocity and a unidirectional block in the transmission of impulse. These conditions can occur as a result of either a depressed fast response or the emergence of a slow response as might occur in a damaged myocardium and/or in response to drug action (6).

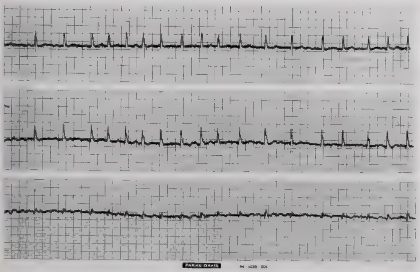

FIG. 1. Shows atrial fibrillation which developed during epidural anesthesia with bupivacaine.

The level of the transmembrane potential (TMP) greatly influences the action potential which follows excitation of the cell. Weidman (7) and Hoffman's group (8–9) have shown when the TMP is near its resting level, the action potential has a rapid rate of rise of phase O (V max) and is of large amplitude and is able more efficiently to excite neighboring tissue and therefore initiate a conducted impulse. When resting potential is reduced (that is, less negative) toward the threshold level, the action potential has a lower V max, a lower amplitude, and is a less effective stimulus to nearby cells.

The electrogenic pump constantly exudes Na^+ from the cell interior and pumps in K^+. It involves Na^+ K^+ activated ATP ase located in the cell membrane. If the pump is partially inhibited (for example, by digitalis), concentration gradients for Na^+ and K^+ are partially dissipated and the resting membrane potential (RMP) is less negative than usual (10). Henn and Sperelakis have shown the depolarization produced by local anesthetics is most likely due to inhibition of the Na^+-K^+ ATP-ase (11).

Disease processes may alter the ionic mechanisms responsible for generation of the action potential and thus convert fast fibers to slow fibers. (12–13). Disease may cause a reduction in the RMP of fast cardiac fibers which in turn inactivates the strong inward sodium current and the fast response. At a RMP of −60mV inactivation is complete and the fast response can not be elicited. Excitation results in regenerative depolarization and an action potential due only to activation of the slow inward current. Electrophysiologic properties of the slow current are tailor-made for the occurrence of dysrhythmias. The rate of depolarization less than 10V/sec and the low amplitude of the action potential result in extremely slow conduction. As Cranefield et al (4) have shown, the slow response is often associated with unidirectional conduction blocks.

Automaticity may also occur in cardiac fibers which have a significant reduction in resting potential. This has been shown in atrial muscle excised from diseased atria (14).

We could therefore, postulate that the atrial dysrhythmia in this patient occurred because of the superimposed effect of bupivacaine in a cardiac fiber already partially depolarized because of ischemic heart disease. Reversion to normal occurred when the effects of the local anesthetic wore off.

The pharmacokinetics of bupivacaine during epidural blockade have been studied by Stanton-Hicks and his colleagues (15) in five healthy male volunteers aged 19 to 25 years. Mean arterial concentrations reached maximum at about 20 minutes after injection and then fell at a decreasing rate until between 120 to 180 minutes post injection when a plateau occurred. For the next 180 minutes of their experiment, there was only a very small fall in the arterial concentration of bupivacaine. In this study, epinephrine 1:200,000 was added to the bupivacaine solution. This has been shown to lower blood levels of bupivacaine (16). Since plasma protein binding may be decreased in older persons, a higher concentration of free local anesthetic would be expected with a slower fall in plasma concentration (17). These factors would be expected to cause a shift to the right in the time-concentration curve in our patient.

Alterations in the repolarization phase of the cardiac action potential which are independent of changes in depolarization may in certain circumstances be dysrhythmogenic (18). In our patient, it is also possible that oscillations of the membrane potential during repolarization in an damaged myocardium might be brought to threshold by catecholamine release (a result of attempted compensation for sympathetic blockade in the area of epidural anesthesia) with resultant tachydysrhythmia. This seems less likely in view of the time course.

Direct intravascular injection with a toxic reaction to bupivacaine seems even less likely. There was an adequate level of anesthesia which lasted the usual period of time for bupivacaine.

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Ovarian Hemangioma With Acute Abdominal Pain

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Abstract

Hemangioma of the ovary is reported in a 53-year-old woman. This patient had acute right lower quadrant pain secondary to torsion of the ovarian tumor. This is the third reported case of this complication with ovarian hemangioma.

We recently observed a patient with nausea, vomiting and acute right lower quadrant abdominal pain caused by a large cavernous hemangioma of the right ovary; a common symptom complex from an unusual cause.

Case Report

The patient, a 53-year-old (para 1, gravida 1), postmenopausal female (menses started at age 12), was admitted to Long Beach Memorial Hospital with a twelve-hour history of severe right lower quadrant pain, nausea and vomiting. The patient's last menstrual period was five years prior to admission. She had one prior hospital admission for upper gastrointestinal bleeding. She also had a long history of alcoholism.

The following abnormalities were found when physical and pelvic examinations were performed: 1) a tender, ballotable, rounded mass of 14 cm in diameter was felt in the right lower abdominal quadrant and right adnexae; 2) the liver was enlarged by percussion and palpation to 12 cm below the right costal margin.

The following laboratory studies were either negative or within normal limits: blood urea nitrogen, two hour postprandial blood sugar, electrolytes, uric acid, creatinine, alkaline phosphatase, lactic dehydrogenase, creatine kinase, transaminase calcium, phosphorous, amylase, lipase, alpha fetal globulin, fibrinogen, activated partial thromboplastin time, prothrombin time, urinalysis and a pregnancy test. The hemoglobin, hematocrit, red blood cell and platelet count were within normal limits. The white blood count was 13,000 per mm^3 with 70% segmented neutrophils and 2% nonsegmented neutrophils.

Abdominal ultrasound examination showed a large cystic mass in the right lower abdomen. An intravenous pyelogram and lower gastrointestinal barium study were unrevealing.

An exploratory laparotomy was performed on the day after admission. When the abdomen was opened, a large, right ovarian mass was found. There was evidence of torsion of 360° at the hilum of the right ovary with complete obstruction of the right ovarian blood supply. A bilateral salpingo-oophorectomy and total hysterectomy was then performed. The patient recovered from the operation without difficulty and was discharged from the hospital twelve days after admission.

Gross examination of the operative specimen showed an 18 × 14 cm right ovarian tumor that weighed 1500 grams. The surface of the tumor was bossed and irregular. On cut section, the tumor was hemorrhagic, necrotic and compartmentalized into cystic cavities of 1 to 7 centimeters. The cavities contained hemorrhagic fluid under pressure. Microscopically, the tumor was composed of large, dilated, thin walled spaces lined by endothelium and filled with blood. The interlacing parenchyma was hyperemic and ne-

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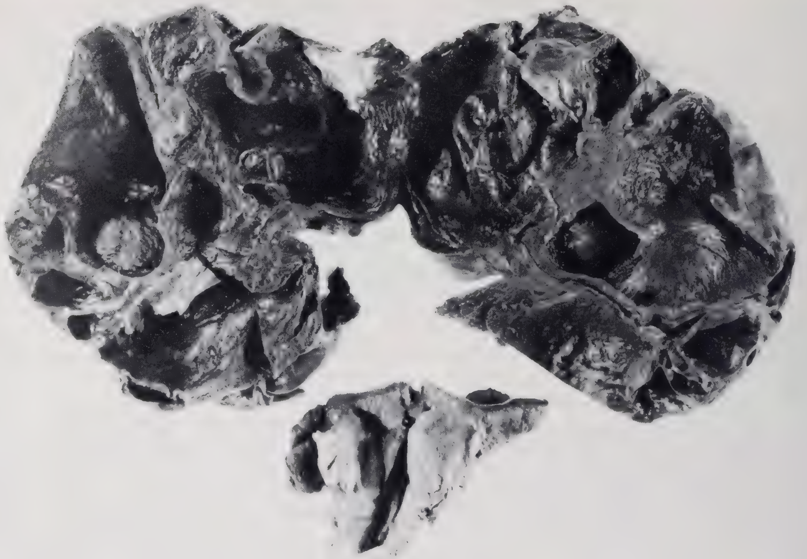

FIG. 1. *Gross photo of right ovary bisected and uterus.* The right ovary is markedly enlarged and measuring 18 × 14 cm. On section of the ovary, the entire specimen is replaced by a multiloculated tumor mass showing extensive hemorrhage and necrosis. The uterus is grossly unremarkable.

crotic. The remainder of the specimen showed a superficial cervical erosion, an endocervical polyp and chronic cervicitis. The left fallopian tube and ovary were normal.

Discussion

Cavernous hemangiomas rarely occur in the ovary. The first report of this lesion in the ovary was by Payne (1) in 1969. Since that time, less than thirty cases have been described (2–10).

Ovarian hemangiomas are usually unilateral. Bilateral tumors were found in only four cases. Two of these (1, 11) were associated with generalized hemangiomatosis, while a third case (6) was associated with a cervical hemangioma. One patient had a unilateral ovarian hemangioma without other organ involvement and thus resembled most reported cases in this aspect.

The age of reported patients with ovarian hemangiomas has ranged from three and a half months to sixty-three years, but the tumor was found more commonly in patients under the age of thirty. Our patient was fifty-three when the hemangioma was discovered.

In about two-thirds of the reported cases, the tumor has been found as an asymptomatic incidental finding at either autopsy or surgery. Eight patients, however, have had symptoms. Two patients had abdominal pain due to torsion of the tumor (12, 13). Three patients had abdominal swelling due to ascites (14–16) and three patients had abdominal discomfort due to the presence of the ovarian mass (3, 5, 11). Our patient, the third case, where symptoms were due to torsion of the hemangioma.

Summary

Hemangioma of the ovary is reported in a 53-year-old woman. This patient had acute right lower quadrant pain secondary to torsion of the ovarian tumor. This is the third reported case of this complication with ovarian hemangioma.

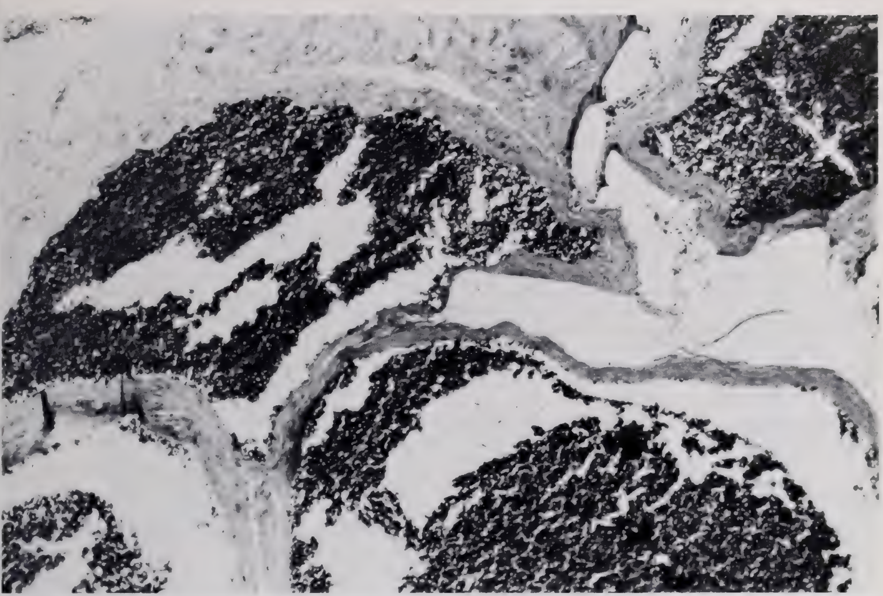

FIG. 2. *Microscopic examination of the tumor.* Microscopic examination of the ovarian tumor (×400) reveals it to be composed of large, dilated, thin walled spaces which are lined by endothelium and filled with blood. Fibrous septa separate these blood filled spaces.

Acknowledgments

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Endobronchial Actinomycosis

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Abstract

We report the findings in a 16-year-old diabetic boy with pulmonary consolidation, cavitation, and an endobronchial mass visualized at flexible fiberoptic bronchoscopy. The diagnosis of actinomycosis was made from histologic sections of a bronchial biopsy. The endobronchial mass was caused by extension of intrapulmonary disease to the bronchial submucosa. Actinomycosis is a rare cause of an endobronchial mass and can be diagnosed from histologic sections and anaerobic cultures.

Involvement of major bronchi in actinomycosis is rare. We report the clinical and pathologic findings in a 16-year-old diabetic boy with a bronchoscopically visible endobronchial mass due to actinomycosis.

Case Report

A 16-year-old boy from the Dominican Republic was admitted to the Mount Sinai Services-City Hospital Center at Elmhurst, New York, August 9, 1980, with a history of left anterior pleuritic chest pain and hemoptysis for two weeks. The patient was an insulin-dependent diabetic since he was five-years old and had a six-year history of recurrent hemoptysis and left upper lobe consolidation. Six and four years prior to admission he underwent flexible fiberoptic bronchoscopies which showed no abnormality. On both occasions bronchial washings and cultures for bacteria, mycobacteria, and fungi were negative. The presumptive diagnosis was bronchiectasis and recurrent pneumonia of the left upper lobe. Intermediate strength tuberculin skin tests showed less than 10 mm of induration on several occasions. The patient denied any history of weight loss, night sweats, exposure to tuberculosis, loss of consciousness, foul-smelling sputum, recent dental work, facial trauma, or shortness of breath. His physical examination was normal except for a rectal temperature of 101° F and slightly decreased breaths sounds over the left upper lung field.

His laboratory work showed a white blood cell count of 10,700/cu mm with a normal differential count, erythrocyte sedimentation rate of 74 mm/hour, glucose 395 mg/100 ml, and urinalysis 4+ glucose/3+ ketones. His chest x-ray showed dense consolidation with cavitation in the left upper lobe (Fig. 1). A gram stain of the sputum showed many polymorphonuclear leukocytes without predominant organisms. A repeat intermediate strength tuberculin test showed 15 mm of induration. Flexible fiberoptic bronchoscopy demonstrated a small pale endobronchial mass with intact mucosa in the anterior segment of the left upper lobe. Biopsy of this endobronchial mass resulted in the release of a small amount of purulent material but bacterial cultures were negative. Histologic sections demonstrated multiple organized granules composed of densely tangled gram positive filaments typical of actinomyces in the bronchial submucosa (Figs. 2, 3). Acid fast stains were negative. Computerized axial tomography confirmed the presence of multiple cavities within the area of consolidation plus left pleural thickening without rib or chest wall involvement. The patient was initially treated with intravenous penicillin 4 million units every six hours. Isoniazid and rifampin were given because of recent tuberculin conversion. Rifampin was discontinued after cultures for tuberculosis were reported negative. Significant clinical and chest x-ray improvement after three months of high dose intravenous penicillin supported the diagnosis of actinomycosis.

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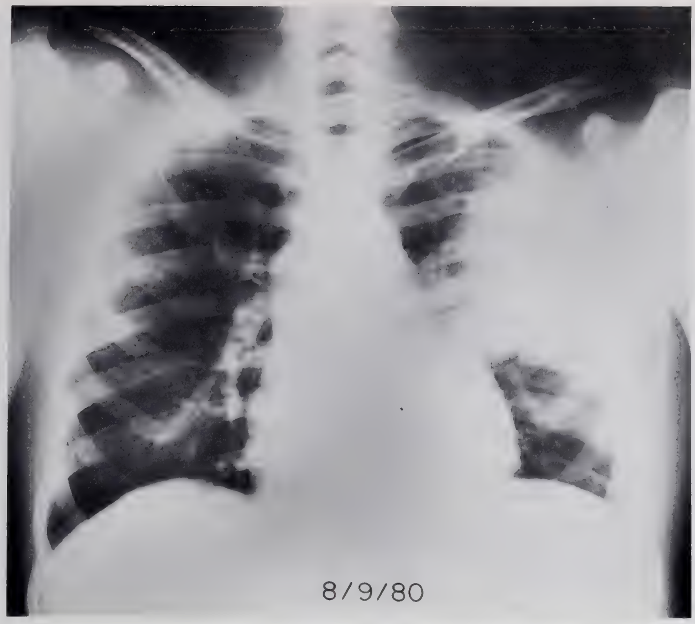

FIG. 1. Chest x-ray taken on admission showing dense consolidation and cavitation in the left upper lobe.

Discussion

This patient with poorly controlled diabetes mellitus, longstanding lung disease, presumably bronchiectasis, and recent tuberculin conversion, developed recurrent pulmonary consolidation and cavitation in the left upper lobe. Actinomycosis was not suspected even after visualization of the endobronchial mass at fiberoptic bronchoscopy. The diagnosis of actinomycosis was made from histologic sections of the bronchial biopsy, and supported by clinical and radiologic response to high dose intravenous penicillin. Failure to grow the organism was probably due to not obtaining anaerobic cultures.

Actinomyces is a gram positive, branching, filamentous, anaerobic, non-acid-fast bacteria which forms sulfur granules. It is a normal inhabitant of the oral cavity. Pulmonary involvement occurs in 20 percent of all cases and usually results from aspiration or, less commonly, direct extension from abdominal or cervicofacial actinomycosis (1). Propagation of infection probably requires the presence of damaged lung tissue. Our patient had uncontrolled diabetes mellitus and a pre-existing lung condition, probably bronchiectasis, which may have set the stage for the development of actinomycosis. However, the possibility of chronic pulmonary actinomycosis cannot be excluded. Brown (2) reviewed antecedent factors and associated diseases in 181 patients with actinomycosis, including six with diabetes mellitus. No relationship between actinomycosis and diabetes mellitus was found.

Primary pulmonary actinomycosis usually presents as a peripheral lesion either in a small bronchiole or in the lung parenchyma (1). It characteristically extends to the pleural cavity and chest wall, resulting in empyema, sinus tracts, and osteomyelitis of ribs. In rare cases, infection may spread into a major bronchus and produce a bronchial mass visible by bronchoscopy. Biopsy of such a bronchial mass may reveal either actinomycosis (3), as in our patient, or chronic inflammatory fibrosis (4, 5).

Cope (6) described superficial bronchitis caused by actinomycosis. Bates and Cruickshank (1) believe that an anaerobic infection cannot be confined to the wall of a bronchus without disease in the adjacent lung. There is no record of a primary

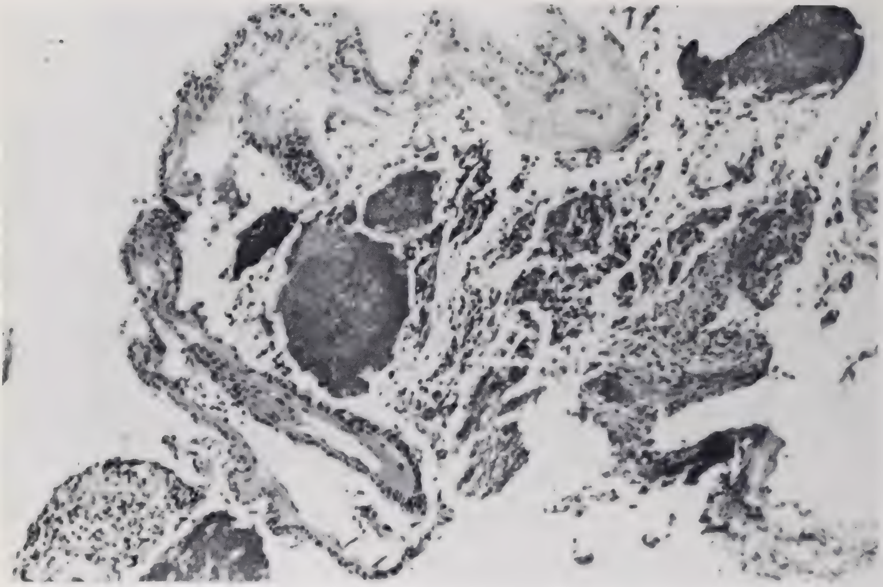

FIG. 2. Multiple granules with inflammatory cells in the bronchial submucosa (hematoxylin and eosin stain ×100).

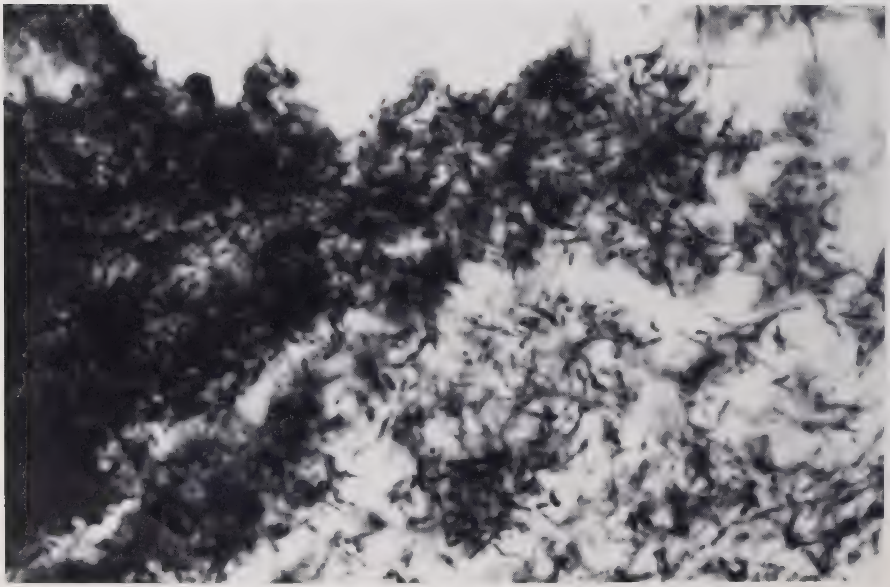

FIG. 3. Granules containing gram positive branching filaments (gram stain ×800).

bronchial infection extending into surrounding lung. In our patient, the endobronchial mass presumably resulted from extension of intrapulmonary disease into the bronchial submucosa.

Finding Actinomyces israelii in sputum or bronchoscopic aspirate does not necessarily prove the presence of actinomycosis since this organism may be a normal inhabitant of the mouth. The radiographic identification of pulmonary infiltrates, empyema, sinus tracts, and rib osteomyelitis is suggestive of actinomycosis but not specific (5). Only culture or microscopic visualization of actinomyces organisms in infected tissue is proof of disease. Therefore, aggressive diagnostic methods such as bronchial biopsy, percutaneous needle biopsy, transbronchial lung biopsy, or open lung biopsy are required. Penicillin in high doses, given over an extended period of months, is the drug of choice. Our patient responded to intravenous penicillin alone and did not require surgery.

Although major bronchus involvement in actinomycosis is rare, the histologic findings of bronchial biopsy may be diagnostic. Actinomycosis should be considered in the differential diagnosis of an endobronchial mass.

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Is A Gastric Drainage Procedure Necessary after Proximal Gastrectomy or Esophagogastrectomy?

B. CH. GOLEMATIS, M.D., P. G. DELIKARIS, M.D., G. N. BONATSOS, M.D., AND M. C. DOUZINAS, M.D.

Abstract

A gastric drainage procedure seems to be necessary with the esophagogastrostomy because of the inevitable incidental bilateral truncal vagotomy that occurs during a proximal gastrectomy or an esophagogastrectomy for carcinoma of the cardia, fundus, or lower esophagus.

Although the limited evidence favors the gastric drainage in such conditions, there is some clinical and experimental work that indicate excellent results when such a drainage procedure is avoided.

During a seven-years period, 14 patients were subject to an esophagogastrectomy for carcinoma of the gastroesophageal junction with restoration of gastrointestinal continuity by an esophagogastrostomy without a drainage. Clinical assessment with radiologic and endoscopic examinations of our patients at three different time intervals after the operation indicated that drainage was not necessary and that the majority of the patients were symptom-free with no evidence of gastric retention or any problem of gastric emptying.

Introduction

Bilateral truncal vagotomy should be considered inevitable during proximal gastrectomy or esophagogastrectomy for carcinoma of the cardia, fundus or lower esophagus. In addition, since Dragstedt and Shafer in 1945 clearly defined the complications of vagotomy without drainage (4), it has been generally accepted that such procedures should be complemented by gastric drainage.

The Heineke-Mikulicz pyloroplasty, with the Ramstedt pyloromyotomy as an adequate alternative have been, for years, the answer for the anticipated stasis in the gastric remnant (antrum) when the latter was anastomosed with the proximal esophagus. However, in the last two decades, there have been reports in the literature both from clinical (1, 2, 5, 8, 10) and experimental data (9) to show that such a pyloroplasty is probably unnecessary.

This is a retrospective study of a limited number of our patients in whom gastrointestinal continuity following esophagogastrectomy for carcinoma of the gastroesophageal junction was restored by esophagogastrostomy without a pyloroplasty.

Patients and Methods

During the years 1971 to 1978, 14 patients with carcinoma of the gastroesophageal junction had esophagogastrectomy followed by esophagogastrostomy without pyloroplasty. The anastomosis had been an end-to-side on the anterior gastric wall in one layer continuous dexon 2.0 reinforced by two silk 2.0 stay sutures at the corners (Fig. 1).

There were ten males with age ranging from 52 to 73 (mean 64.6) and four females with age ranging from 56 to 71 years (mean 62.4). There was no operative mortality. These patients were evaluated at three and twelve months after the operation and recently three to nine years postoperatively. Evaluation included only clinical assessment at the first interview, while radiologic and endoscopic examination were performed at subsequent follow-up.

Results

At three-month period, all patients seemed to be well. There was no clinical evidence of gastric

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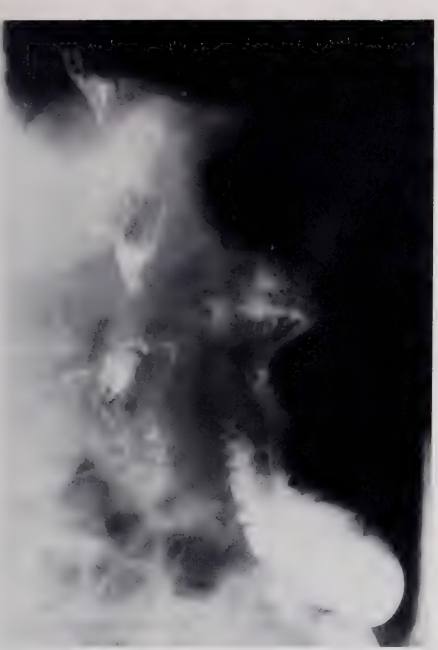

FIG. 1. One layer end-to-side esophagogastro anastomosis on the anterior wall of the gastric remnant following esophagogastrectomy without drainage.

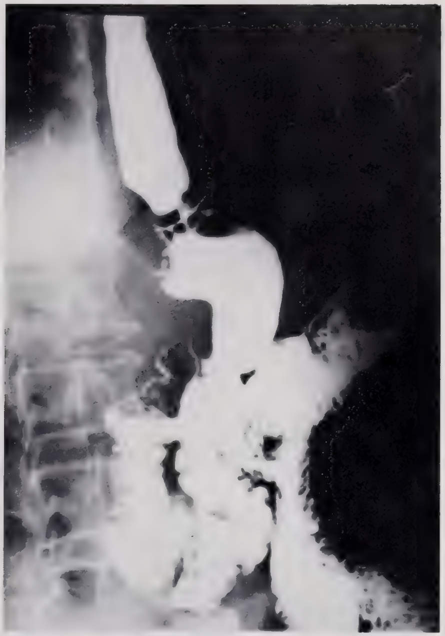

FIG. 2. Radiologic examination (A) 3 months, (B) 12 months, after an esophagogastrectomy with an esophagogastrostomy without a pyloroplasty. Gastric emptying begins within few minutes after swallowing the contrast medium.

stasis. Nine patients had no symptoms. Three patients complained of fullness, and were advised to change the rate and type of meals to more frequent and smaller portions. Two patients had mild diarrhea.

At 12-month follow-up, only 11 patients were evaluated. There was one death due to an unrelated cause and two patients died due to disseminated disease. On clinical assessment, nine of the 11 patients were symptom-free. One patient suffered from mild diarrhea and one regurgitated when lying flat. There was no dysphagia, fullness, dumping or vomiting.

On endoscopy, there was no obvious bile reflux through the intact pylorus. Biopsies of the distal antrum, in seven of the 11 patients examined, showed evidence of atrophic gastritis (grade III-IV) consistent with their age. The mucosa of the distal esophagus was normal in all but two of the patients (one complained of regurgitation) when mild esophagitis was noticed and confirmed on biopsies. Emptying of the stomach seemed to be within normal limits in all patients on radiologic examination after a standard meal with 50 ml of Barium. Barium entered the duodenum within the first few minutes after the patients swallowed the contrast (Fig. 2). All stomachs were completely empty of contrast within six hours from the onset of the examination.

Six patients, surviving three to nine years after the operation, were examined recently. These patients were symptom-free. Endoscopy and biopsies of the prepyloric antrum revealed moderate to severe atrophic gastritis in all of them, while four patients showed mild to moderate esophagitis on biopsies of the distal esophagus.

Radiologic examination showed no evidence of gastric retention or any problem in gastric emptying.

Discussion

Standard surgical technique dictate that esophagogastrostomy following esophagogastrec-

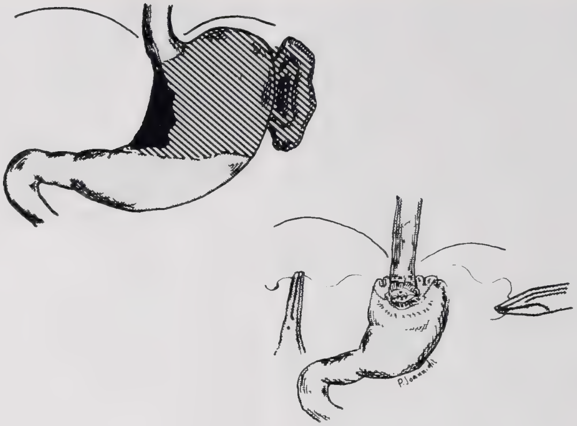

FIG. 3

tomy be combined with a gastric drainage procedure because of the invariable parasympathetic gastric denervation following any operation in which the lower esophagus is resected (3, 7). However, there is very little evidence that such a procedure is really necessary. On the contrary, the work of Zacho and Fischermann (10) based on 86 patients clearly indicated that drainage in unnecessary since the vast majority of patients did very well without it.

This concept was reinforced seven years later by the experimental work of Shapiro (9). Studies of gastric emptying in 12 mongrel dogs who had undergone vagotomy and esophagogastrostomy with and without pyloroplasty showed no difference between the two groups. In 1975 Angorn reviewed excellent results from ten of his patients in whom gastric drainage was not performed (1), and recently Ellis concludes from the review of 27 out of 72 patients who did not have a gastric drainage that such a procedure is not always necessary (6). Postoperative retention was noticed in only three patients who subsequently had a pyloroplasty.

The results of our small series clearly indicates that at least in some of these patients gastric drainage is unnecessary after esophagogastrectomy and esophagogastrostomy. None of the few clinical complaints could be attributed to the lack of emptying. Fullness could be attributed to the decreased capacity of the gastric reservoir and regurgitation to the absence of the lower esophageal sphincter. The endoscopic findings are not different from these observed in matched groups of patients with similar operations and from the radiologic studies, gastric retention with stasis could be excluded. In addition all the problems that can arise by damaging the pyloric sphincter are obviously avoided, that is, immediate post-operative complications, dumping, bile reflux, and, according to Ellis and Gibb, it is very doubtful whether gastric drainage influences the anastomotic integrity (6).

What would the reason be for the adequate emptying of the antrum in those cases of vagotomy without drainage? Apart from the possible activation of the independent antrum's pacesetter potential (9) one could think of the beneficial influence that the change of the antrum's position that allows gravity to play a more significant role in the gastric emptying. Finally, and if one believes that some patients will develop retention at the end and will demand a gastric drainage (6), the establishment of the criteria for those who will need a pyloroplasty seems mandatory so that these patients can have their drainage procedure at the first stage.

Summary

Despite the inevitable incidental bilateral truncal vagotomy during esophagogastrectomy, good post-operative results as defined by clinical assessment, radiologic and endoscopic examina-

tion were observed in patients in whom such a procedure was not carried out. A gastric drainage procedure appears unnecessary in at least the majority of cases.

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Radiation Injury to Small Intestine

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Abstract

Radiation induced stricture of the small intestine occurs in less than 0.5 percent of patients receiving abdominal or pelvic radiation. The incidence, etiology, and pathogenesis of the disease are discussed. The clinical courses of all three patients reported were marked by latent periods varying from 30 months to fourteen years, multiple remissions and exacerbations and variable response to nonoperative therapy. Six operative procedures were performed in these three patients. Anastomotic dehiscence was not seen. Recurrent stricture occurred in two of three patients. In one patient, a reticulum cell sarcoma was found within the confines of the radiation stricture.

An adequate trial of nonoperative management is recommended in view of the frequent remissions and exacerbations, as well as a significant incidence of recurrent stricture following surgery. At operation limited dissection of irradiated bowel is advised.

Stenotic lesions of the small bowel provide a therapeutic challenge in the management of patients with radiation injury of the gastrointestinal tract. The rarity of these lesions does not permit any individual surgeon to have more than limited experience in dealing with this problem. Although the difficulty in managing these cases is uniformly recognized, opinion regarding the choice and timing of surgical procedure is often divergent. It is the purpose of this communication to report three cases of radiation-induced strictures of the small bowel recently treated at The Mount Sinai Medical Center.

Case Reports

Case #1

A 74-year-old white male was treated with 6000 rads of tele-cobalt therapy following incomplete removal of a prostatic carcinoma. Bilateral orchiectomy was performed two years later for the control of the local disease and estrogen therapy was started. Thirty months following the radiation therapy, the patient developed partial small bowel obstruction which was treated successfully with long intestinal tube decompression. A barium enema (Fig. 1) as well as small bowel series (Fig. 2) confirmed the presence of stricture in the terminal ileum. While inhospital, a recurrent episode of small bowel obstruction ensued. This failed to respond to long tube decompression. At operation, a localized stricture was found in the distal ileum 3.5 feet from ileocecal valve. A segmental resection of small bowel with end-to-end anastomosis was carried out. Dense fibrosis and chronic ulceration were noted on gross examination. Histologic examination revealed radiation vasculitis, and stricture formation. In addition, a reticulum cell sarcoma was present at the site of the stricture. The lymph nodes were not involved. The patient has remained well during the 42-month follow-up period.

Case #2

A 43-year-old white female had radiation therapy following removal of ovarian carcinoma in 1958. She developed small bowel obstruction in 1972. Radiation stricture of the terminal ileum was noted at operation and a side-to-side ileotransverse colostomy performed. Fourteen months later, the patient developed another episode of partial small bowel obstruction which responded successfully to long intestinal tube decompression. In April, 1976, she again developed an episode of small bowel obstruction. A barium

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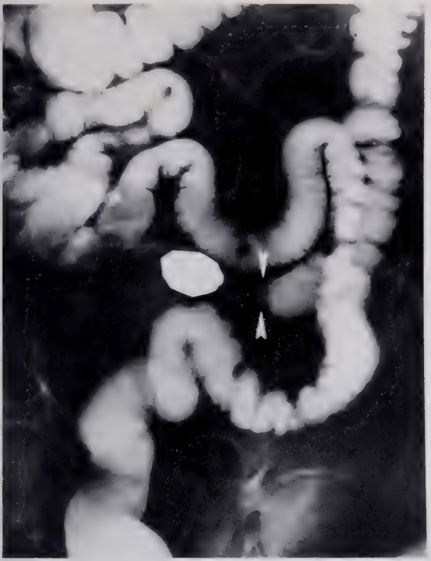

Figure 1. Barium enema with reflux into the terminal ileum demonstrating stricture (indicated by arrow) in the terminal ileum.

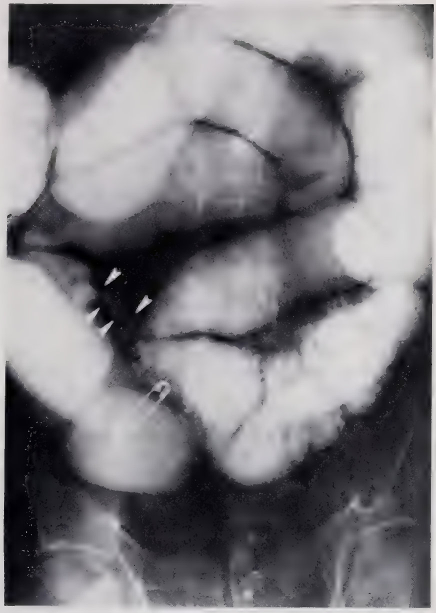

Figure 2. Small bowel series demonstrating dilated bowel proximal to the stricture (indicated by arrow) in terminal ileum.

enema at this time showed narrowing of the previous ileo-transverse colon anastomosis with dilatation of the proximal small bowel. Long intestinal tube decompression was unsuccessful. At operation, she was found to have distal ileum matted and firmly adherent to the pelvic peritoneum. The previous ileotransverse colon anastomosis was narrowed. This segment was resected and a side-to-side ileotransverse colostomy performed. She remained well for approximately six months. Abdominal cramps and vomiting progressively increased and she was readmitted in April, 1977 with small bowel obstruction. Radiographic examination of the colon again showed narrowing of the ileotransverse colostomy. Dilatation of small bowel proximal to the anastomosis was noted. Long intestinal tube decompression was attempted unsuccessfully. At operation, stenosis of the previous ileotransverse colostomy was noted and a large side-to-side ileotransverse colostomy was constructed proximal to the previous anastomosis. She has remained well during the 22 months following the operation.

Case #3

A 54-year-old white male was previously diagnosed as having a seminoma of the left testicle at age 34. Treatment in 1958 included left orchiectomy and retroperitoneal lymph node dissection followed by tele-cobalt therapy. Terminal ileal obstruction due to radiation injury became manifest four years after the radiotherapy. Resection of a 40 cm segment of thickened fibrotic terminal ileum with end-to-side ileo-ascending colostomy was performed at this time. This patient remained well until June, 1977, when he developed mild intermittent crampy abdominal pain which was treated symptomatically. In June, 1978 he was admitted with partial small bowel obstruction. This responded only temporarily to decompression with a nasogastric tube. Radiographic examination of the small intestine revealed marked dilatation of the small bowel. At operation stenosis of the previous ileo-ascending colostomy was found to be the cause of obstruction. A side-to-side ileotransverse colostomy was performed. The patient remained well during the eight months following operation.

Discussion

The overall incidence of bowel injury following radiation for pelvic malignancy is in the range of 2% to 3% (1). Although early reports indicated an incidence as high as 17% (2), most series published in the last 25 years report bowel injury to be below 3% (1–4). The small intestine is the site of injury in 1% to 2% of patients receiving radiotherapy for pelvic malignancy (1, 5). The incidence of serious small bowel complications seems to have increased in the last several years (6, 7) and higher total radiation dosages and supravoltage therapy is generally held responsible for this increase. Small bowel strictures were not recognized as a manifestation of radiation injury until 1934 when Jones reported the first case of radiation-induced stricture of the small bowel (8). The incidence of such stricture is now believed to be less than 0.5% (2–4, 9).

The most important determinant of radiation injury to the bowel is the total dose of radiation delivered (7, 10–13). Significant risk of small bowel injury exists at dosages above 5000 rads.

The small intestine is known to be more sensitive than the colon to the effects of irradiation, but perpetual free movement of its loops seems to impart a protective effect. A previous laparotomy or pelvic operation and pelvic infections may cause fixation of the small intestine into the field of irradiation (1, 14–18) with resulting predisposition to radiation injury (9, 15, 19). Such predisposition existed in two of our three cases.

The gross pathologic findings are surprisingly constant. The ileum, especially the terminal ileum, is affected in the large majority of the cases (20). The site of the lesion in all three cases in this series was the long segment of bowel which looked pale, edematous and thickened. Telangiectatic vessels may be present on the surface. The mesentery may be edematous, thickened and foreshortened. Milky chylous fluid secondary to partial lymphatic blockage may be present in the peritoneum.

The pathogenesis of these lesions may be broadly classified into three phases (19): 1) edema and hyperemia, 2) ulceration, and 3) stricture formation. The earliest stage is that of acute inflammation and is manifested by edema, hyperemia, and spasm, usually reaching its maximum in 3 to 4 weeks after irradiation. During this period, suppression of mitosis and reduction of crypt cell activity occur. Cell damage and death are most pronounced in proliferating crypt cells. Submucosa and subserosa become congested and edematous with dilated lymphatics and fibrinoid material. Thereafter changes subside in the majority of instances and healing occurs without obvious alteration in structure and function. The lesions may progress with endarteritis and thrombosis of the vessels of the bowel wall causing mucosal infarction and ulceration of varying degrees. These ulcers may be single or confluent and multiple. They may be confined to the mucosa or extend through all layers of the bowel wall. They may perforate into peritoneum or penetrate into adjacent viscera. Healing of these ulcers may result in fibrosis and cicatrization with progressive narrowing of the intestinal lumen. Hyaline deposits frequently increase the width of the submucosa and subserosa. Sclerosis is less marked in the arteries than in the veins which show obliterative endophlebitis. Lymphatic and venous ectasia provide striking features. Muscle cells show edema, degeneration and atrophy with fibrosis and hyaline degeneration. The mucosa also shows atrophic features at this stage. Risk of oncogenesis in radiation exposure has long been recognized (21, 22). Somatic mutation is suggested to be responsible for such malignant transformation (23). Several cases of colorectal cancer following pelvic radiation have been reported (24–31). The interval between irradiation and appearance of *biopsy-proven* carcinoma has ranged between 1 and 25 years in these cases. Radiation induced cancer of small intestine has not been previously reported to the best of our knowledge. Experimental evidence of radiation induced oncogenesis in small bowel has, however, been demonstrated. Irradiation of exteriorized small intestine in rats produces a high incidence (67% of survivors) of low grade adenocarcinoma (32). Fast neutron irradiation (270 rads) is also known to produce a high incidence of intestinal tumors (33). Presence of reticulum cell sarcoma within the radiation-induced stricture observed in one of our patients is an interesting and noteworthy association. Although, a fortuitous association cannot be excluded, a causal relationship is suggested by presence of the tumor within the area of stricture with histologic changes of radiation enteritis (Fig. 3).

These patients usually present with the clinical features of partial or complete intestinal obstruction. Significant radiation injury to small bowel is usually manifested within the first two years

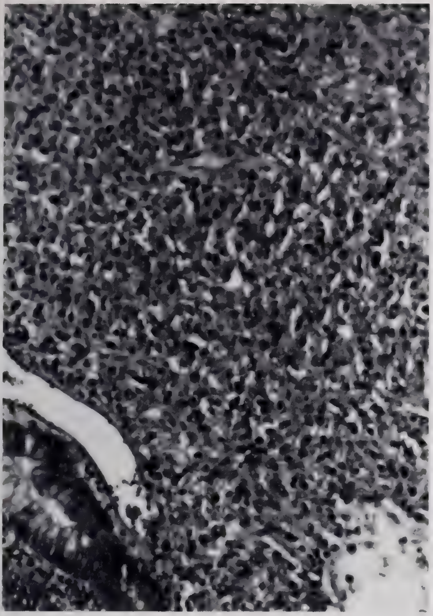

Figure 3. Photomicrograph demonstrating reticulum cell sarcoma within the confines of radiation-induced stricture.

(34, 35). Friedman (20) reported the onset of symptoms six to twelve months following radiation. The latent period in most series is less than two years. Isolated cases with latent periods up to 32 years have been reported (36-38). The latent interval was 14 years in one of our cases. In the remaining two it was less than four years.

Malnutrition with anemia and hypoalbuminemia is more common when long segments of small bowel have sustained radiation injury. Malabsorption and decreased dietary intake are probably both responsible (37). Steatorrhoea is not uncommon.

Although signs of intestinal obstruction may be obvious on conventional abdominal radiographs, barium examination of the small bowel may help to localize the site of stenosis. Puddling of barium in the terminal ileum or segmental saw-tooth-appearance of small bowel is commonly seen. Rigidity of the small intestine with destruction of the normal mucosal pattern may occur. Often, the radiographic appearance of the small intestine is normal (39).

Some principles of management in cases of radiation induced intestinal strictures appear well established. Surgery for relatively minor symptoms should be avoided and aggressive nonoperative management must receive adequate trial before operative intervention is contemplated. Kawarda et al (35) were able to successfully treat nearly half of their patients with long tube intestinal decompression alone. Others, however, believe that management of radiation induced small bowel injuries almost always requires operative intervention (14).

It has been postulated that local intestinal ischemia, poor tissue healing and general malnutrition contribute to the relatively high incidence of anastomotic dehiscence, reported to occur in 10 to 25 percent of the cases (9, 19, 40). This problem is compounded by the radiation enteritis which may be more extensive than is evident on gross inspection at operation and may eventuate in recurrent strictures at the suture line even though the anastomosis has been placed through apparently normal bowel.

The variable and unpredictable pathologic changes in the gastrointestinal tract as a result of exposure to irradiation have created uncertainties for surgeons as to the need for surgical intervention, it proper timing, and the extent of the procedure, that is, bypass without resection (15, 16) vrsus wide resection and anastomosis (1, 16, 19, 34, 41). Recurrent stenosis was observed by Shamblin et al (19) in 25% of their cases. Our personal experience is too small to determine whether bypass or resection is preferable. We did not observe any anastomotic dehiscence. It is disconcerting, however, that in two of the three cases presently reported, anastomotic stricture recurred. In these two patients, radiation induced strictures had been treated by wide resection and end-to-end anastomosis. In one case restenosis occurred twice.

Several principles in technical management of these problems appear clear: 1) When the patient is severely malnourished or the small bowel is grossly distended because of prolonged obstruction, bypass without resection is preferable to minimize the extent of surgery and to avoid the placement of suture lines through chronically distended intestine. 2) Adhesions of loops of intestine should not be dissected unless it is planned to resect the involved bowel. The sites of minimal serosal trauma may eventuate in perforation and fistula formation. 3) Sites selected for anastomosis should have frozen section review to determine whether or not microscopic evidence of radiation enteritis is present (41, 42). 4) Prior to surgery, a long intestinal tube should be passed. This should be positioned by operation and be allowed to remain for several days after surgery to permit adequate decompression of the small bowel.

Terminal ileal lesions account for the most frequent site affected and deserve special mention. Involvement is often diffuse, affecting several inches of terminal ileum. Occasionally there are multiple strictures in this area. In such instances, bypass of the involved terminal ileum, with ileotransverse colostomy (15, 40, 43) may be the procedure of choice. The transverse colon is preferred as the site of anastomosis because the cecum and ascending colon are usually heavily exposed to radiation. Several authors (44–46) have noted that the terminal ileal lesions may be quite localized and permit a limited resection with end-to-end anastomosis. This was possible in one of our cases.

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Neurologic-Neurosurgical Notes

Alan E. Rubinstein, M.D. and Martin H. Savitz, M.D.,
Coeditors

Unusual Presentation Of Herniated Intervertebral Disc: Report Of Two Cases

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Abstract

Two cases of extruded discs presented with symptoms, signs, and neuroradiologic evidence of an intradural neoplasm. The differential diagnoses of the myelograms are discussed. The operative findings are described.

Introduction

Two patients were admitted to the hospital with neurologic symptoms and signs of a spinal tumor. In each case, myelography was consistent with an intradural mass (1). At the time of surgery, both lesions were found to be extruded disc material in the anterior epidural space.

Case Reports

Case 1. A 36-year-old woman noted the onset of stiffness in her neck and pain radiating to her right shoulder about eight weeks prior to admission. Intermittent cervical traction and an anti-inflammatory agent were prescribed by her family physician. Approximately two weeks later, she developed spasticity in both legs, as well as numbness in the medial aspect of the right hand. When her walking deteriorated, she was referred to a neurologist. She specifically denied any injury to the cervical area. There was no bowel or bladder dysfunction. Her past medical history revealed benign cysts of both breasts.

Significant findings in her physical examination were confined to the neurologic examination. Sensory testing elicited a level of hypesthesia up to the C 7 dermatome. Deep tendon reflexes were hyperactive in the lower extremities. Babinski's sign was present on the right side. Her gait was broad-based.

X-rays of the cervical spine were unremarkable. A cervical myelogram was performed after injection of ethyl iodophenylundecylate at the L4-5 level. With the patient in the prone Trendelenburg position, a complete block to the cephalad flow of contrast material was demonstrated at the C 7 level. In the frontal projection (Fig. 1a), the shadow of the spinal cord was not widened but apparently displaced from right to left. In the lateral view (Fig. 1b.), posterior displacement of the cord shadow seemed to be consistent with an intradural extramedullary lesion located anteriorly. The cerebrospinal fluid protein was elevated at 70 mg%. The differential diagnoses were: 1) meningioma, 2) metastasis, 3) neurofibroma, and 4) arachnoid cyst.

Neurosurgical consultation was requested. The patient underwent complete laminectomy from T1 through C5. The dura was opened, and the spinal cord was observed to be of normal shape and configuration. The flow of cerebrospinal fluid from above was scant. The anterior dura was noted to be somewhat devascularized and firm in consistency. After gentle displacement of the cord, the anterior dura on the right side was incised. Degenerative disc material immediately

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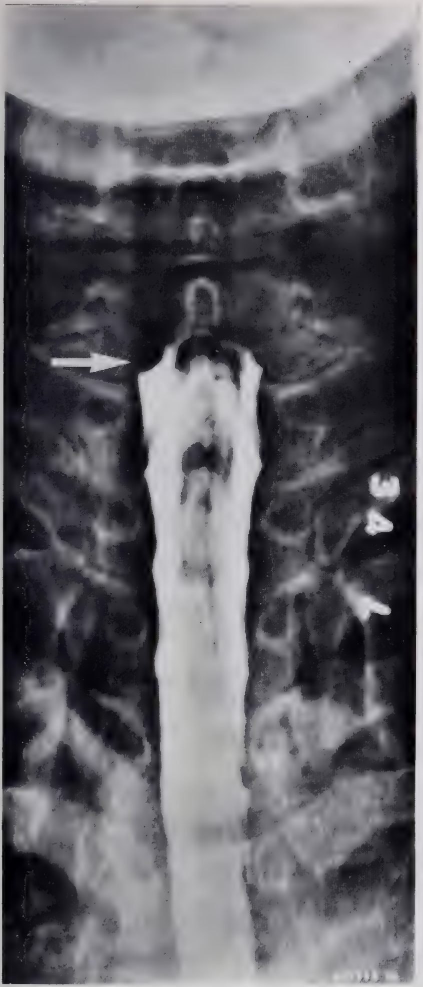

FIG. 1a. Frontal projection of complete block at C7 level. Note cord shadow is not enlarged, but the subarachnoid space is wider on the right (arrow) than on the left.

and spontaneously extruded. The left side was then explored by a similar incision, and extruded disc material was removed with a small pituitary rongeur.

Postoperatively, the patient became free of pain. Over a period of six months, her neurologic examination returned to normal. One year following surgery, she was asymptomatic.

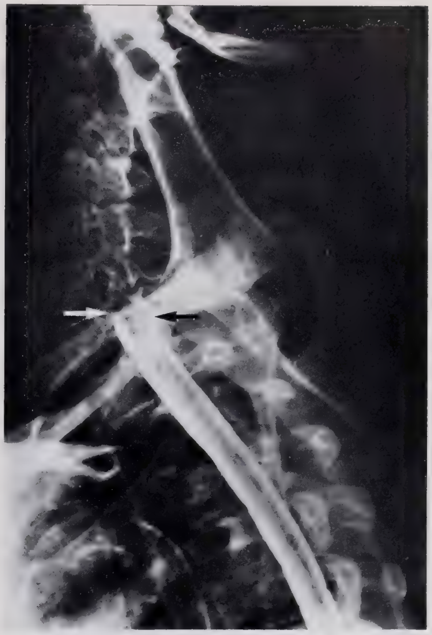

FIG. 1b. Lateral view of cuplike block (arrow). Note sharply delineated borders showing posterior displacement of the spinal cord and mimicking an intradural lesion located anteriorly.

Case 2. A 28-year-old man gave a 4-month history of difficulty in starting urination and in maintaining an erection. He was initially treated by a urologist. Eight weeks later, he was referred to a neurologist when he developed numbness and weakness in the right calf and foot. He denied any trauma. Past medical history was unremarkable.

Significant findings in his physical examination were confined to the neurologic examination. Bilateral foot drop and weakness of the knee flexors and extensors were demonstrated. There was hypesthesia in the L5 and S1 dermatomes. The Achilles reflexes were absent.

X-rays of the lumbosacral spine were unremarkable. A lumbar myelogram was performed after injection of metrizamide at the L3-4 level. With the patient in a prone erect position, a complete block to the caudad flow of contrast material was demonstrated at the L4 level in the frontal projection (Fig. 2a.). In the lateral view (Fig. 2b.),

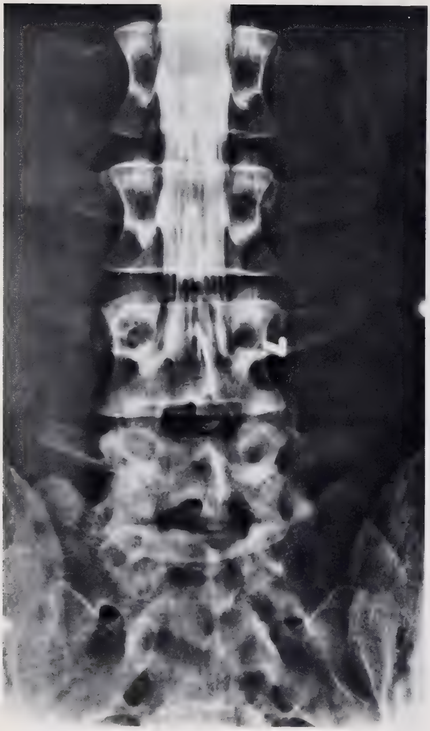

FIG. 2a. Frontal projection of complete block at L4 level (left marker). Note that the nerve roots are not displaced.

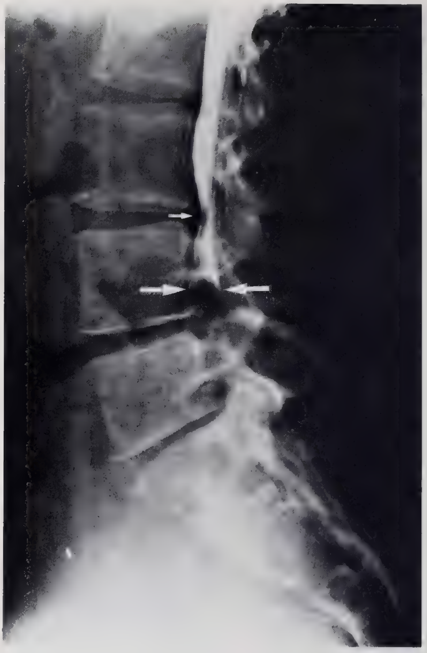

FIG. 2b. Lateral view of capping lesion with sharply outlined corners (large arrows) intruding into opaque column. Note incidental disc bulging (small arrow) at the L3–4 level.

a smoothly outlined negative shadow, unrelated to the disc space, was interpreted as an intradural neoplasm. The cerebrospinal fluid protein was elevated at 44 mg%. The diagnoses considered were: 1) neurofibroma, 2) ependymoma of the cauda equina, and 3) arachnoiditis.

Neurosurgical consultation was requested. The patient underwent complete laminectomy from L5 through L3. The entire thecal sac was observed to be herniating posteriorly. The epidural space was investigated anteriorly. One large and two smaller fragments of extruded disc material were removed with a pituitary rongeur. Exploration of the L4-5 disc space was performed, and no further herniated nucleus pulposus was found.

Postoperatively, the patient became free of pain. Bladder and sexual function returned to normal. One year after surgery, he was asymptomatic.

Discussion

Clinical diagnosis with localization of tumors of the spinal cord, nerve root, meninges, and surrounding tissue is sometimes possible; but the signs and symptoms of other disease processes may mimic a neoplasm (2). Myelography utilizing positive contrast media is the most widely accepted diagnostic procedure for identification and precise localization of spinal lesions (3). The absence of any trauma or infection and the increase of neurologic symptoms and signs over a period of months favored the diagnosis of a neoplasm. Plain x-rays of the spine failed to demonstrate any widening of the spinal canal, enlargement of the intervertebral foramina, collapse of the disc space, or abnormal calcification. The myelograms were consistent with intradural tumors. Elevated cerebrospinal fluid protein may be found with any manometric block. The unusual presentations of these two herniated intervertebral discs illustrate the difficulty in establishing exact criteria to distinguish an extradural lesion from an intradural lesion.

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Student's Corner

Lawrence Eichenfield, Editor

Postoperative Myocardial Infarction Following Noncardiac Surgery: A Case Report

BRIAN DOUGLAS HERSHEY

Abstract

The case of a 69-year-old gentleman who underwent surgery for intermittent claudication is presented. The patient had experienced three myocardial infarctions and had suffered from angina for twenty years. In addition, triple vessel coronary artery disease had been demonstrated by angiography eight years prior to surgery. Postoperatively, the patient developed a myocardial infarction (MI) and expired.

Risk factors for postoperative myocardial infarction were reviewed. No information was found on the risk represented by multiple myocardial infarctions and the literature devoted to angina as a risk factor was inconclusive. Many risk factors are clearly defined in the literature, but these do not apply to the patient.

The current methods of assessing surgical risk were applied to this case and it was found that, although the patient was a Class IV risk according to the criteria of the American Society of Anesthesiologists (ASA) because of his cardiac disease, he met none of the criteria for the risk factors in the Goldman Cardiac Risk Index (CRI). It is concluded that: 1) the risk as assessed by the ASA criteria and the CRI can be widely disparate, even when the high risk assessment by the ASA criteria is due to cardiac disease, 2) further research is indicated to assess the risk of postoperative MI associated with severe angina and multiple myocardial infarctions and, 3) modification of the Cardiac Risk Index may be indicated to include a consideration of severe angina and multiple myocardial infarctions.

Introduction

The occurrence of myocardial infarction after noncardiac surgery is of concern to both the surgeon and the anesthesiologist because of the threat that it represents to the patient's life. Improvements in surgical and anesthetic technique have led to surgical intervention in increasingly ill and aged patients. Considerable attention has, therefore, been paid to defining the incidence, risks and morbidity of postoperative myocardial infarction (MI) in noncardiac surgical patients.

The case of a patient who sustained postoperative myocardial infarction is presented below in the framework of the existing literature. The risk factors for this phenomenon will be emphasized.

Case Report

This patient is a 69-year-old gentleman who presented with a history of intermittent claudication in both legs, of four-years duration, which had grown more severe in the year prior to admission. He had had three myocardial infarctions at four, three and one year(s) prior to admission, and a twenty-year history of angina pectoris. This had been stable in the few months prior to admission, although the threshold for angina was low and there was occasional nocturnal pain. Angiography performed eight years prior to admission showed severe triple vessel disease. In addition, the patient had adult onset diabetes mellitus for many years for which he received an oral hypoglycemic drug. He had undergone cholecystectomy, appendectomy and hemorrhoidectomy, all of which were performed many years prior to admission, under general anesthesia, without complications.

His medical regimen at the time of admission included: isosorbide dinitrate (Isordil 5 mg sublingual as needed and Isordil-SA 40 mg at bedtime), digoxin (0.25 mg each day), nitroglycerin (Nitropaste 2½ inches at bedtime), propranolol (Inderal 40 mg four times daily), dipyridamole (Persantine 50 mg twice daily), furosemide (Lasix 80 mg once daily), potassium chloride (8 m Eq daily), and imipramine (Tofranil 25 mg four times daily). The patient also received quinidine (200 mg three times daily), although the indication for this medication was not clear from the history.

Physical examination revealed a chronically ill patient. There was a II/VI systolic ejection murmur, loudest at the 2nd right anterior intercostal space. Peripheral pulses were diminished or absent in both legs. An electrocardiogram (EKG) on admission showed bradycardia, old inferior wall myocardial infarction, and nonspecific ST-T wave changes in the precordial leads. The chest x-ray was within normal limits. The hematocrit was 39.5.

A translumbar aortogram showed reconstructable arterial disease and the patient was scheduled for a right axillary bifemoral bypass. The patient was classified as a group IV risk by the American Society of Anesthesiologists (ASA) criteria and premedicated with diazepam (Valium) 15 mg.

The operation required two hours and its course was uneventful. The patient was induced with Thiopentol 200 mg. D-tubocurare 6 mg and succinyl choline 100 mg were used in the intubation and the patient was ventilated by a semiclosed circular circuit with a tidal volume of 700 ml and a respiratory rate of 12 breaths per minute. Maintenance was achieved with nitrous oxide (4 liters/min), oxygen (2 liters/min) and one percent Ethrane. Heparin (5000 units) was administered intraoperatively and reversed with protamine sulfate (25 mg over 15 minutes). During surgery, he received one liter of replacement fluid, the estimated blood loss being 250 ml. Blood pressure and pulse were stable throughout the operation at 120/60 and 60 respectively. The patient was slightly pale, although stable in the recovery room and returned to his floor two hours postoperatively.

Three hours postoperatively, the patient developed "knot-like" substernal pain radiating to the right arm, unrelieved by nitroglycerin. Bibasilar rales, a heart rate of 86 beats/minute and a blood pressure of 115/80 were noted. There was no jugular vein distension or peripheral edema. The EKG showed a normal sinus rhythm, ST depression, tall T waves in leads V_1 and V_2 and small R waves in leads V_1 to V_3. The next day, new Q waves were noted in leads V_2 through V_6. Creatine kinase and the CK:MB fraction were elevated. Lactate dehydrogenase (LDH) was also elevated, although LDH 1:2 was negative. The patient was transferred to the cardiac care unit where his condition deteriorated. He experienced repeated episodes of chest pain. The bibasilar rales persisted. On the seventh postoperative day, the patient experienced a cardiac arrest from which he could not be resuscitated.

Literature Review

Among unselected patients undergoing major noncardiac surgery, the reported incidence of postoperative MI ranges from 0.66% to 2.4% (1−4). When all types of surgical procedures are considered, the incidence of postoperative MI decreases greatly (5).

However, certain patients are at greater risk for postoperative myocardial infarction. The evidence is convincing that preoperative MI represents one of the gravest risk factors for postoperative MI. Among patients who had experienced preoperative MI, Topkins and Artusio found the incidence of postoperative reinfarction to be 6.5%, which represents a tenfold increase in the incidence of postoperative MI over patients without a previous MI (1). This is in agreement with the study of Tarhan et al who found the incidence of postoperative reinfarctions to be 6.6% (6).

The interval between the infarction and the surgery has been shown to be significant. Topkins and Artusio found that 54.5% of patients in their series with an MI in the past six months experience reinfarction after surgery (1). This decreased to 1.0% when the MI occurred more than three years before surgery. Goldman et al found an MI within the past six months to be a statistically significant risk factor for postoperative cardiac death. They also found that the risk of cardiac death to a patient with an MI between one and six months prior to surgery is not significantly lower than that for a patient who has had an infarction within four weeks of surgery. After an interval of six months has passed, they found no increase in the incidence of MI compared to patients who have never had an MI (1.3%) (8). Other studies have found reinfarction to occur in 27% to 37% of patients who have had an infarction within the three months prior to surgery, while the rate of reinfarction stabilized at 4% to 5% if the interval was six months or greater (6, 9).

Patients with specific EKG abnormalities preoperatively are also at increased risk for postoperative myocardial infarctions. Goldman et al found that an episode of more than five premature ventricular contractions (PVC) at any time in the past is a significant risk factor for cardiac death, perhaps as a marker of severe cardiac disease (8). A rhythm other than sinus or the presence of premature atrial contractions also represent risk factors. They found no correlation between postoperative MI and abnormal QRS complexes, ST segments or T waves. Mauney et al, in their study of 365 patients over 50 years of age with EKG changes of previous MI, bundle branch block, left ventricular strain or hypertrophy, or ST signs of subendocardial injury found 18% of their patients showed new or additional signs of ischemia postoperatively, including 8% with acute MI (10). In another series, 75% of the patients who developed postoperative infarctions had abnormal preoperative EKGs (3). Conversely, Rosen et al observed that two of their three patients who experienced postoperative MIs (in a series of 506 operations) had normal preoperative EKGs (11). Nonetheless, preoperative EKG abnormalities appear to identify patients who are at an increased risk of developing postoperative infarction.

Ischemic heart disease may itself represent a risk for the subsequent development of postoperative MI. Two studies indicate that patients with coronary artery disease are more likely to develop postoperative ischemic EKG changes (11, 12). Two others indicate that such patients are at no greater risk or only slightly greater risk for postoperative MI (8, 19). Mahar et al report that three vessel coronary artery disease represents a risk factor which is significantly reduced by artery bypass graft. In their series, three of fifteen patients with three vessel coronary artery disease experienced postoperative myocardial infarction (13). Other studies further demonstrate that patients who have undergone coronary artery bypass graft are not at greater risk than the general population of surgical patients, although they do not demonstrate that the pre-existing coronary artery disease was a risk factor; that is, that these patients were at greater risk before the bypass graft (14, 15). Nonetheless, along with Mahar et al, they suggest that coronary artery bypass graft may be beneficial before other forms of surgery. The literature, however, contains no reports of the efficacy of "protective" coronary artery bypass grafts.

Patients with a history of heart failure are at greater risk for cardiac complications postoperatively (16, 17). Nonetheless, Goldman et al have found that the presence of clinical failure at operation does not increase cardiac risk unless a third heart sound or jugular vein distension are present (7).

Valvular heart disease also appears to be a risk factor. Goldman et al report that a systolic ejection murmur louder than Grade II/VI with corroborative signs of aortic stenosis represents a risk (7) and, elsewhere, they report that a Grade II/VI or louder murmur of mitral regurgitation also represents a risk (8).

Preoperative hypertension was reported to cause an increased risk of postoperative MI in two series (9, 11), but not in three others (8, 16, 18). Diabetes mellitus apparently plays no role in postoperative MI (8–10, 16). Smoking, glucose intolerance, hyperlipidemia and peripheral vascular disease also represent no risk (8). Several studies show that age represents a risk factor (3, 7, 11). However, one study found postoperative reinfarction to be no more frequent in people over 60-years old (9). Females were shown to be at risk in two studies (11, 19), but not in two others (7, 9). Goldman et al have found the emergent nature of the procedure and the patient's preoperative health to be significant risk factors (7).

Much research has been done to assess the risk factors associated with the surgery itself. The type of anesthesia has consistently been demonstrated to have no impact upon the incidence of postoperative MI (1, 2, 4, 6, 9). Intrathoracic and abdominal surgery cause an increased risk of postoperative cardiac complications (6, 9) as does aortic surgery (10). Fraser et al found no MIs among patients undergoing minor procedures (20). The duration of surgery has been found to present no increased risk in otherwise healthy patients (1, 2, 6, 8). However, in two studies of patients with other preoperative risk factors, the duration of surgery was found to increase the risk of postoperative MI (9, 10). Profound and enduring intra-operative hypotension was found to be a significant risk factor in several studies (5, 9, 10).

Available data agree that most postoperative MIs occur within the first three days after surgery (2, 5, 6, 9). There is also agreement that postoperative reinfarction carries with it a greater mortality rate than a postoperative infarction without a previous MI. Reports of the mortality of postoperative MI in patients with a previous MI range from 53%–70%, whereas in patients without a previous MI, it is 26.5% (1, 6, 10). The extent of myocardial damage influences mortality. Arkins et al found the mortality rate to be 77% for transmural infarction and only 7% for subendocardial infarcts (19).

In summary, recent myocardial infarctions, certain EKG abnormalities, intraoperative hypotension, and the site of surgery represent the greatest risk factors for postoperative MI. A recent study has implicated certain signs of congestive heart failure, certain types of valvular heart disease, the patient's preoperative health and the emergent nature of the operation as risk factors for postoperative cardiac mortality. Ischemic heart disease may predispose to postoperative MI, but coronary artery bypass graft negates the risk. Age has been shown to be a risk, although the role of hypertension, the duration of surgery, and female sex is uncertain. There is no evidence to demonstrate that diabetes mellitus, smoking, hyperlipidemia, peripheral vascular disease, and choice of anesthetic agent represent risk factors for postoperative myocardial infarction.

Discussion

Many factors contribute to make surgery a particularly dangerous undertaking in the patient at risk for cardiac complications. Myocardial oxygen demand may be increased secondary to tachyarrhythmias, volume overload, hypertension or catecholamine release at the time of surgery. Concomitantly, the oxygen delivery to the heart may be compromised by intraoperative hypotension, diminished cardiac output due to arrhythmias or anesthetic agents, hypovolemia, anemia, or inadequate oxygenation. Even intubation has been associated with ischemic EKG changes (12). It is therefore important to identify those patients who are less able to tolerate these demands on the myocardium.

This patient would be categorized as a Class I risk according to the Goldman Cardiac Risk Index (CRI), the most comprehensive means of assessing risk factors for postoperative cardiac complications, as he manifested none of the risk factors defined by the authors (7). In Goldman's series, 0.2% of surgical patients who fell into this group suffered postoperative cardiac death. Interestingly, the patient narrowly missed meeting the criteria for three risk factors: that is, he was 69-years old (not over 70), he had surgery done on the femoral arteries (not the aorta itself), and he had a II/VI systolic ejection murmur heard loudest at the aortic area (and, although there were no other signs or symptoms of aortic stenosis, "important aortic stenosis" was never ruled out). In addition, the patient was taking quinidine on admission, presumably for an unidentified arrhythmia. If, in the past, he had previously experienced five or more premature ventricular contractions, this would have increased the risk as assessed by the CRI considerably. This case points out two of the difficulties encountered in trying to apply the CRI clinically: there is no allowance for "borderline-positive" risk factors (is age 70 a greater risk factor than age 69?) and the clinician must often work in the absence of clinically pertinent information (what was this patient's history of arrhythmia?).

The patient presented with one risk not considered in the CRI, namely, three vessel coronary artery disease (13). In addition, his history of three previous myocardial infarctions is remarkable, although the literature offers no data on the risk represented by multiple infarctions. The most recent MI, one year prior to admission, is well-removed from the six-month risk period proposed by several researchers (6, 7, 9). Lastly, an interesting incongruity is observed in this case. According to the ASA criteria, this patient is classified as Class IV risk as a result of cardiac disease. Class IV is the penultimate risk category reserved for patients who are severely incapacitated by life-threatening disease. This is true and, yet, by CRI criteria, the patient is assessed to be in the most favorable risk category.

The soundest approach to the management of postoperative myocardial infarction appears to be careful preoperative identification of patients at risk. Close cardiopulmonary monitoring of such patients may serve to provide an early warning of impending MI and permit more prompt intervention. Furthermore, delay of surgery, to obtain better medical control of risk factors or to permit more time to pass between the time of surgery and a previous MI, may be an option worth considering in less urgent cases. Both alternatives depend upon recognition of the patient at risk. The review of the literature has demonstrated that there are many factors which represent profound risks: for example, recent MI, clinical signs of heart failure and certain arrhythmias. Nevertheless, the patient presented provides a thought-provoking example of a patient who, despite a history of repeated myocardial infarctions and widespread atherosclerotic disease, seems to elude the criteria defined in the literature of a patient at risk for postoperative MI. The reluctance of surgeons to operate on patients with angina accounts for the paucity of studies of postoperative MI in patients with angina. Indeed, Goldman et al, in their paper describing the CRI, specifically note that there were too few patients with Class IV angina to constitute a statistically significant sample (7).

In conclusion, three important points emerge; namely, that 1) the risk as assessed by the CRI and the ASA classification can be widely disparate, even when the high risk assessment by the ASA classification is the result of cardiac disease; 2) further research is indicated to identify the risk of postoperative MI associated with severe angina and multiple myocardial infarctions and, 3) modification of the Cardiac Risk Index may be indicated to include a consideration of severe angina and multiple myocardial infarctions.

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Trachoma

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Abstract

This author spent five weeks in the Sudan treating and studying patients with trachoma. The paper presents the historical and cultural perspectives of the treatment program. In addition, the pathogenesis, clinical course, and epidemiology of this chlamydial infection are described. The paper concludes with personal observations about the control of the disease and the current relevance of chlamydial infections.

Introduction

In recent years, there has been a great deal of interest in the diseases caused by chlamydia. It is recognized that a larger and growing spectrum of diseases is due to these unique organisms (1). Trachoma, the leading cause of preventable blindness in the world, is a chronic keratoconjunctivitis due to a complex bacterial-chlamydial interaction. This ocular infection afflicts 400,000,000 people, primarily in North Africa, the Middle East, and parts of Asia, where the disease is endemic (2). Though trachoma has an ancient history of plaguing mankind, our knowledge of the pathogenesis, immunology, and course of the disease is still evolving.

I spent five weeks during the summer of 1981 treating and studying trachoma in the Sudan, where the disease is endemic. I participated in a World Health Organization-United Nations project along with several other medical students and physicians from the Sudan and America. The project was a continuation of a 10-year mass treatment program in the Northern Province. Our main objective was to treat as many patients as possible as we travelled through the villages along the River Nile.

The dynamics of treating trachoma in this area of the world are greatly influenced by cultural and historical forces. The Sudan is the largest country in Africa, much of the land being desert, some of which is made livable by water from the River Nile. The River is formed at Khartoum by the joining of the Blue Nile (from Lake Rudolf in Ethiopia) and the White Nile (from Lake Victoria in Kenya). It flows downstream through the Northern Province to its mouth in Cairo. The Province is entirely desert where temperatures soar to 125°F and only several kilometers on each side of the Nile is inhabited. It was here that the Nubian people settled 6000 years ago to take advantage of the small strip of arable land along the River. Every year around August the Nile floods its banks depositing a copious amount of silt which has, and continues to, sustain life for this ancient people. The area is part of the "fertile crescent," thought to be the cradle of civilization.

The Nubians live today much the same way they did 6000 years ago. They speak an ancient language, use primitive methods of farming, and live in mud huts that protect against the intense sun. Sanitation is primitive. People defecate into buckets where rats, lizards, and insects feed from the fecal material and create a reservoir for disease. Western concepts of hygiene are nonexistent. Contamination of the water supply is inevitable; disease is spread by people drinking from common cisterns of water that often comes unfiltered from the Nile. Consequently, communicable and tropical diseases are the scourge of the Nubian civilization much the same way they were thousands of years ago. Trachoma, typhoid fever, diptheria, malaria, schistosomiasis, etc. plague the population. Filariasis (River Blindness) is also endemic in parts of the Sudan. Combined with trachoma, the threat of blindness is a great fear of the people. Infant mortality is very high and life expectancy is only fifty years. Food is not plentiful but starvation, kwashiokor, and marasmus are rare because the people share.

Biology of Chlamydial Infections (Trachoma)

The genus chlamydia, formerly known as bedsonia, is comprised of a large group of intracellular parasites. In this way they are similar to viruses but, like bacteria, they contain both RNA and DNA, a gram-negative like cell wall, ribosomes, and they divide by binary fission. Some

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researchers compare these unique organisms to gram-negative bacteria that differ only in that they lack certain enzymes necessary for independent energy metabolism (3). Chlamydia are taken up by phagocytosis and then rapidly grow and divide. Eventually this process permits the visualization of a large characteristic inclusion body. It lies near the nucleus and stains deep purple with Giemsa stain.

All chlamydia share certain characteristics in their morphology, including a group antigen. There are two species- c. psittaci and c. trachomatis. The latter contains two strains that infect humans exclusively, and cause lymphogranuloma venereum (LGV). C. psittaci strains infect birds and animals primarily; humans are accidental hosts. Non-LGV strains of c. trachomatis are the etiologic agents implicated in nongonnococcal urethritis in men, inclusion conjunctivitis in newborns and adults, infections of the female genital tract, epididymitis, and endemic and nonendemic trachoma (4). Of these diseases, trachoma afflicts the greatest number of people worldwide. The large spectrum of chlamydial diseases is thought to result from a combination of antigenic variation and environmental influences.

The pathogenesis and clinical course of the disease has been studied extensively. There is some confusion regarding the classification of the stages of the disease in different textbooks. In the Sudan, we utilized the World Health Organization classification system based upon conjunctival changes. It does not take into account the degree of disability but was useful in terms of treatment. The description of trachoma that follows is a result of my experience combined with the knowledge I gained from Sudanese physicians.

One to ten days postinfection with c. trachomatis (via eye to eye contact through fomites, hands, and flies), a purulent nonspecific conjunctivitis occurs. The hot, sandy, and dry climate combined with poor hygiene are conducive to the production of conjunctival inflammation and, if a person seeks treatment, he will usually be given chloramphenicol drops in the eye. If the patient does not respond within three weeks, he is thought to have trachoma unless proven otherwise. If trachoma is present, within three weeks of the conjunctivitis a bilateral conjunctival folliculitis occurs (Stage 1). A few small white follicles appear along the lateral fossa of the upper tarsal plate. The follicles will increase in size and number over the next few months if left untreated. As the disease progresses, papillae form on the follicles (Stage 2). These follicles are hypertrophied conjunctival cells and are caused by a secondary superimposed bacterial infection. Implicated agents are usually normal flora, primarily streptococci and staphylcocci. Apparantly, the chlamydia lower the natural resistance of the eye. During Stage 2, the patient may also develop a pannus that eventually may cover the upper limbus of the cornea. Composed of a membrane of granulation tissue, it is heavily invested with blood vessels which obscure the cornea and pupil. A pannus is characteristic of trachoma but not unique to the disease.

If the patient still remains untreated, the follicles will become necrotic and progress to scars over a period of months to years (Stage 3). During Stage 3, scars streak the lateral fossa and may become large enough to cover the entire conjunctiva. Follicles, papillae, and a pannus may all be present bilaterally. Eventually, all the follicles will be replaced by scar tissue (Stage 4 or healed trachoma).

A major complication of trachoma is the scratching of the cornea by the scarred conjunctiva which can lead to corneal ulcers. These ulcers, when healed, form pit-like structures that are clearly visible to the examiner and are known as "Herbert's pits." This is the pathognomonic lesion of trachoma. Blindness may occur at any stage because of the corneal pannus and ulcers. Essentially, the disease is reversible during the first three stages by antimicrobial therapy and/or surgery. Ulcerations and pitting are an irreversible destructive process. Another complication is the formation of an entropion and trichiasis during Stages 3 and 4. These refer to the inversion of the eyelid and eyelashes, respectively, and are the result of intense scarring. This further abrades the eyeball and complicates corneal ulceration.

Epidemiology

My experience in the Sudan indicated that trachoma usually begins insidiously in early childhood, although infection is possible at any age. The disease is rarely diagnosed, if at all, until a child enters school due to the isolated lives of the Sudanese. It is contagious during the first three stages. As much as 90% of the population of the Northern Province are infected, although less than 10% have an active disease. About 3% of those infected will have blinding complications. Immunity to c. trachomatis is unclear, although some form of natural resistance is obviously at play to protect most individuals from the active disease. Immunity to reinfection is unlikely although subsequent attacks are believed to be less severe. The degree of pathology appears to depend upon the mode of infection, the environment, and the type of secondary bacterial infection.

Treatment

C. trachomatis strains and the superinfecting bacteria can be suppressed by sulfonamides, tetracycline, or erythromycin. Both oral and topical modalities have been proven effective. Drug resistant strains have not been isolated. Mass treatment programs, like the one in the Sudan, utilize a 30-day regimen of 1% tetracycline ointment applied once a day. This has proven far simpler and more effective than the older method of using oral sulfonamides. Oral erythromycin has also proven effective in large scale programs.

In recent years, there has been interest in the production of vaccines to protect against chlamydial infections. Although antiserums have been developed, their use has not been successful because of a high rate of adverse reactions.

In the Sudan, the treatment program is aimed at primary school children. Usually, 5th graders are taught about the disease and how to apply the ointment on each other. For 30 days, time is set aside during school hours to allow the children to apply the drug. In addition, the children are given free soap and instructed on good hygiene. According to Sudanese health officials, the on-going program has been successful in reducing the incidence and prevalence of trachoma and its complications. No figures have yet been compiled.

Conclusion

Worldwide, endemic trachoma is disappearing. This is primarily due to the rapid modernization of the underdeveloped countries. Taiwan and Yugoslavia are excellent examples of nations that have virtually eliminated trachoma. But many countries such as the Sudan remain very poor and must rely upon antimicrobial therapy as the mainstay of treatment for the disease. At best, these are stopgap measures aimed at decreasing the chances of blinding complications. Any attempt to erradicate the disease is unrealistic at this time. A 30-day regimen of tetracycline offers only six months of protection against reinfection. Unfortunately, without concurrent economic expansion, improvements in the health status of the Sudanese people are likely to be minimal. Any changes in the lives of the people might also be slow to occur since life there is steeped in ancient traditions and beliefs that in themselves may be adaptive, but may promote infectious disease.

Recently, there has been evidence to suggest that classic trachoma is occurring with an increased frequency in nonendemic areas (5). The genital infection caused by c. trachomatis has been shown to be transmissible to the eye via the birth canal or from vaginal-ocular contact. The development of classic trachoma in this way has been termed paratrachoma or genital trachoma (6). Furthermore, there is data to suggest that inclusion conjunctivitis is not such a different disease than trachoma. These two diseases are from the same organism and may be merely different stages of the same pathologic process (7). Paratrachoma is not clustered among patients of a lower socioeconomic status as is the case with trachoma. Several cases among the children of medical personnel have been reported (8).

With an increasing amount of c. trachomatis infection being identified, it is important for physicians to discard the old notion that trachoma does not occur in the western industrialized countries. Physicians need to familiarize themselves with the clinical aspects of the disease in order not to delay treatment.

Acknowledgments

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The Epidemiology of Cardiovascular Disease and Diabetes Mellitus in Perspective

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The heart and major arteries are major sites of disease in contemporary medicine. Fatty deposits or atheroma narrow the channels or increase the vulnerability to complete closure with major consequences for the end-organs supplied. Involvement of the coronary, cerebral or peripheral arteries, particularly to the lower limbs, result in angina pectoris and myocardial infarction, transient ischemic attacks and strokes, and intermittent claudication and gangrene of the toes or feet, respectively. The pathologic sequence and resultant clinical disease occur both in the diabetic and nondiabetic. The differences between the two in terms of their relative frequencies and the source of the excess incidence in the diabetic is the subject of this meeting. Microvascular conditions that are more specific to diabetes, such as the characteristic diabetic retinopathy will not be considered here, discussions being confined to the macrovascular conditions.

Table I presents a summary adapted from Knowles et al in the report of the National Commission on Diabetes in 1975 (1). It provides an abstract of the literature on the frequency of coronary disease since 1930. Coronary disease in diabetics occurs twice as frequently as in nondiabetic controls. Clinical studies have also examined the alternative situation, that is, the occurrence of diabetes or glucose intolerance in patients with coronary artery disease. Table II, assembled by Falsetti and Schnatz (2), shows the extraordinary frequency of glucose intolerance in patients with coronary heart disease whether diagnosed clinically or confirmed by angiographic studies. In addition to the increased morbidity associated with diabetes, many studies based both on analysis of death certificates and on autopsies have shown that cardiovascular disease is the prominent cause of the excess mortality in diabetics.

Although the evidence from the literature appears overpowering, nevertheless the data, viewed critically, can only be used to set, not establish, the hypothesis that diabetes is associated with an increased cardiovascular morbidity and mortality. The possible confounding of the results by factors of selection in all of these studies requires the application of more rigorous epidemiologic techniques to examine fully the apparent association.

The use of classical epidemiology for the study of chronic diseases is a comparatively recent development. It was employed initially in this country in the Oxford Diabetes Study in 1946-47 and was followed shortly by the establishment of the well-known heart study in the nearby town of Framingham. Many epidemiologic studies have been conducted since then. In general, the good diabetes studies have inadequate cardiovascular documentation and, conversely, the good cardiovascular studies have inadequate documentation of diabetes. Consequently, gaps in our understanding of the relationship between the two conditions continue at all levels of inquiry.

Two prevalence studies in the 1960's, one in Tecumseh, Michigan (3) and the other in Bedford, England (4), were the first to show that blood glucose may be an independent risk factor for coronary artery disease. This finding remained unsubstantiated for many years and verification through the employment of the complete cardiovascular risk profile or through prospective incidence studies were awaited. An outstanding attempt to correct this deficiency was made by a group of investigators with international repre-

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TABLE I

*Coronary Disease Frequency in Diabetics and Controls**

AUTHOR (YEAR)	GROUP	NO.	CORONARY DISEASE (%)	RATIO
Blotner (1930)	D	77	45	2.1
	C	450	21	
Enklewitz (1934)	D	74	31	1.9
	C	520	16	
Nathanson (1932)	D	74	53	6.6
	C	249	8	
Root (1939)	D	349	51	2.8
	C	3400	18	
Hart (1942)	D	193	46	1.6
	C	2250	29	
Starns (1947)	D	50	75	2.0
	C	400	37	
Clawson (1947)	D	978	18	2.0
	C	24923	9	
Goldenberg (1958)	D	264	50	2.2
	C	3206	23	
Feldman (1954)	D	137	44	2.2
	C		20	
Goodale (1962)	D	65	62	1.7
	C	445	37	

D = diabetic; C = nondiabetic controls

* Modified Knowles et al (1).

sentation. The role of asymptomatic hyperglycemia and coronary heart disease was examined in a total of fifteen studies (5). Table III provides a listing of the studies included in the analysis with the numbers of participants in each. In general, reassuringly high participation rates were achieved by the investigators. The quality of the studies, however, was uneven and ranged from well-defined population-based surveys to less acceptible screening of volunteers. Ideally, the endeavor would have been planned in advance and with a common protocol. It was instead, through force of circumstances, a collection of studies utilizing existing data with the major thrust being an attempt to standardize the analyses of the data. Only men in the 40-59 year old age group were included. Known diabetics and treated hypertensives were handled separately to avoid the possible therapeutic alteration of blood glucose levels.

Since glucose is positively associated with a

TABLE II

Incidence of Glucose Abnormalities in Patients with Coronary Artery Disease

Source	No. Diagnosed Clinically	Glucose Abnormalities
Carlson and Wahlberg (28)	100	56 (56%)
Reaven et al (29)	41	31 (76%)
Hatch et al (30)	24	16 (67%)
	No. Diagnosed by Angiogram	
Herman and Gorlin (4)	135	86 (64%)
Falsetti (3)	27	18 (67%)

TABLE III

International Collaborative Groups (Fifteen Populations)

Study	Year of Baseline Examination	Age at Baseline (yr)	Number of Examinees
Australia	1966	40–59	670
Denmark—40 yr	1976–1977	40	493
Denmark—50	1964	50	407
England	1969	40–59	15,759
Finland—HP	1966–1967	40–59	909
Finland—SI	1966–1972	40–59	3,524
France	1967–1972	42–53	6,843
Ireland	1974	40–54	3,500
Italy	1975–1976	35–59	717
Japan	1975–1976	40, 45, 50	4,847
Scotland	1972	45–64	1,362
Switzerland	1965–1968	40–59	1,575
U.S.—PG	1965–1966	40–64	929
U.S.—WE	1960	42–58	1,737
U.S.—CHA	1967–1973	40–59	8,637

number of known cardiovascular risk factors, a multifactor approach to the analyses was adopted, employing the logistic mode to accommodate the dichotomous response variables. Table IV presents, in modified form, the results obtained by the International Collaborative Group. It shows that the definite myocardial infarction category was not significant for any of the participating studies. Electrocardiographic abnormalities showed a significant relationship to blood glucose levels by criteria in three studies, and by the Pooling Project Major Abnormalities in four studies independent of the effects of age, body mass index, systolic blood pressure, cholesterol, and smoking.

Table V provides the mortality experience for eleven of the studies included based on four to fifteen years of follow-up. No study except that of the Chicago Peoples' Gas Company showed any significant association between coronary heart disease deaths and initial glucose levels. For cardiovascular disease mortality, only two studies showed significance.

The summary conclusions from the fifteen study collaboration are shown in Table VI and can be seen to be largely negative for considering asymptomatic hyperglycemia as a risk factor for coronary heart disease and the major adult cardiovascular diseases.

It may be of value in gaining a perspective of the subject to recall some of the factors that bear on studies utilizing blood glucose levels. For many years it was assumed that the best measure of diabetes was a blood sugar determined after an "adequate" challenge. Glucose or a carbohydrate meal was considered suitable without questioning the effects of either the content or amount on the results. It is now well appreciated that major differences can be attributed to the character and size of the challenge. For example, Table VII shows mean glucose values obtained from 583 ambulatory patients at Boston City Hospital many years ago (6). They were given, in turn, both a 100 gm glucose load and a calculated prepackaged meal. The mean blood glucose differences varied according to the subset of the population examined, but was seen to range from 29.5 to 73.3 mg/dl. Data from another study examined various ways of utilizing postchallenge data and the effect such data handling can have on the prevalence of hyperglycemia (6). Venous whole blood data, shown in Figure 1, were obtained from a random sample of the Sudbury, Massachusetts population who were given a 100 gm oral GTT.

TABLE IV
International Collaborative Group
Relationship of Glucose Level and Prevalence of ECG Abnormalities at Baseline: 1 Value in Multiple Logistic Analysis: 13 Studies, Middle-aged Men, International Collaborative Group

	Definite MI	Whitehall Criteria	US Pooling Project Major Abnormalities
Denmark-40	+	0.12	+
Denmark-50	+	−1.14	−1.28
England	−0.42	0.69	0.74
Finland-HP	−1.75	0.00	−1.95
Finland-SI	0.29	1.89	2.26*
France	0.63	1.61	1.15
Ireland	−0.55	0.48	0.28
Italy	+	−0.28	3.18**
Japan			
Excluding Hypertensives on R_x	+	3.05**	1.80
Including Hypertensives on R_x	+	3.35***	2.42*
Scotland			
Excluding Hypertensives on R_x	+	2.58**	0.51
Including Hypertensives on R_x	+	2.50**	0.10
Switzerland	+	0.69^{++}	0.69^{++}
US-P.G.$^{+++}$	0.60	1.72	0.65
US-CHA	0.40	2.12*	2.28*

* $p < 0.05$, ** $p < 0.01$, *** $p \leq 0.001$

$^{+}$ Less than five cases

$^{++}$ A combination of Whitehall and Pooling Project Major Abnormalities

$^{+++}$ Hypertensives on treatment included

NOTE: In most studies, the variables in the multiple logistic analysis include glucose, age, body mass index, systolic blood pressure, serum cholesterol and smoking.

TABLE V

Relationship of Baseline Glucose Level and Subsequent Mortality: 1 Value in Multiple Logistic Analyses: 11 Studies Middle-Aged Men, International Collaborative Group

Study	Total # of Deaths	All Causes	1 Value Cardiovascular	CHD
Australia	56	0.35	−1.06	0.78
Denmark-50	43	−0.25	-1.11^{+}	0.21^{+}
England	414	−0.45	0.60	1.01
Finland-HP	70	0.72	0.38	0.87
Finland-SI	121	1.01	−0.51	−0.21
France	141	3.39***	0.81	0.40
Scotland				
Excluding hypertensives on R_x	60	1.47	1.94	−0.95
Including hypertensives on R_x	100	1.87	2.19*	−0.05
Switzerland	34	1.67	0.84	++
US-P.G.'s				
Post-Load	116	3.67***	3.42***	3.23**
Casual	190	−1.42	−2.10*	−1.63
US-CHA	169	2.34*	0.45	0.31
US-WE^{+++}	271	−0.91	−0.83	−0.95

* $p < 0.05$, ** $p < 0.01$, *** $p \leq 0.001$

$^{+}$ Combined fatal and non-fatal events

$^{++}$ Less than 10 deaths

$^{+++}$ Hypertensives on treatment included

NOTE: In most studies, the variables in the multiple logistic analysis included glucose, age, body mass index, systolic blood pressure, serum cholesterol and cigarette smoking.

The figures of the USPHS criteria were applied to the results. The prevalence of abnormalities vary from 1.2 percent, when exceeding any three values is required, to 13.8 percent when a single value is required for diagnostic interpretations. We can conclude from these studies that methodology will greatly affect studies of both hyperglycemia and diabetes.

A single postglucose elevation is not an acceptable definition of diabetes mellitus. This fact often creates difficulty because hyperglycemia is the hallmark of diabetes mellitus and studies of hyperglycemia are often considered synonomous with studies of diabetes mellitus. Studies of diabetes, based on a single blood glucose measurement, will, because they are so protocol dependent, give inconsistent results when related to cardiovascular events. On the other hand, a major difference both numerically and conceptually arises when persistent glucose elevations are sought, and the current state of the art would generally accept this requirement as characterizing the diabetic state.

The Framingham Heart Study is of particular interest in this context in that the diagnoses of diabetes required a minimum of two blood glucose elevations for classification and this provides a closer approximation to a definition of diabetes mellitus based on persistent hyperglycemia. Table VIII shows the relative risks for cardiovascular disease mortality and morbidity in both

TABLE VI

International Collaborative Group Conclusions

1. Considered together do not indicate an association between asymptomatic hyperglycemia and CHD that is consistent, strong and graded.
2. They do not consistently show evidence for a threshold relationship, i.e., a consistently positive association between the highest levels of asymptomatic hyperglycemia (e.g. the upper 2.0% −5.0% of the distribution and CHD).
3. The negative results for most of the studies when multivariate analyses were done (including blood cholesterol, blood pressure, cigarette smoking) raise additional questions about the relationship between asymptomatic hyperglycemia and CHD.
4. At this juncture, therefore, asymptomatic hyperglycemia cannot be designated an established risk factor for coronary heart disease and the major adult cardiovascular diseases.

TABLE VII

Meal and Glucose Tolerance Tests in 583 Patients

Patient Status	No.	One Hour Glucose (mg/100 ml)		
		GTT*	MIT**	Difference
Normal	434	124.0 ± 32	94.5 ± 21	29.5
Possible				
Disorders	81	174.8 ± 25	117.4 ± 21	57.4
Diabetics	68	255.2 ± 78	181.9 ± 74	73.3

* Glucose Tolerance Test, ** Meal Tolerance Test (mean ± SD)

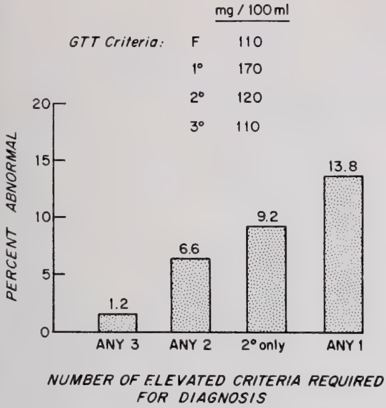

FIG. 1. Effect of varying number of diagnostic criteria.

sexes from this study (7). The risk is, in general, more than doubled in both categories for both sexes. When adjusted for other cardiovascular risk factors, the relative risks weaken somewhat but are still substantial. Another well established feature in the epidemiology of diabetes and cardiovascular evident in this table is the proportionately greater impact that diabetes has in women.

These findings from the Framingham Epidemiologic Study are in accord with findings from the earlier clinical literature referred to previously. How then do we reconcile the largely negative results from the International Collaborative Study in which participants in the highest quintiles had hyperglycemia of considerable proportions (ranging to five hundred mg/dl). The diversity of the studies included in the collaborative analyses must certainly have an effect on their conclusions, disclaimers notwithstanding. The extent of the differences in methods can be noted in Table IX. There were large differences in the size and character of the challenge employed (for example, meal, 50 gm, 75 gm, 100 gm), the sampling time, the specimen analyzed, and the assay method. Such differences in methodology between the studies contribute to the inconsistent results. In addition, many of the studies had relatively few events making the assessment of a possible threshold effect for blood glucose and cardiovascular disease difficult. The presence of such an effect would also question the choice of the linear logistic model for analyzing this data.

Despite any effects such problems may have, the conclusion that diabetes is related to cardiovascular disease but that hyperglycemia, at least as measured at one point in time, is not, must be considered. Such a conclusion would suggest that the other metabolic abnormalities or physiochemical changes associated with diabetes, such as altered viscosity or clotting mechanisms and not the blood sugar level per se, may be the primary problem.

In fact, epidemiologic studies in Busselton (8) and in Helsinki (9), employing multifactor analyses that included blood glucose levels, suggest that the serum insulin level may be an independent risk factor for cardiovascular disease. These are intriguing findiings and will be described in greater depth elsewhere in this symposium.

Summary

Diabetics show an increased cardiovascular morbidity and mortality with a higher occurance appearing in women. The methodology employed in the published studies are very diverse and have questionable effects on the conclusions. Currently

TABLE VIII

Relative Risks of Cardiovascular (CV) Events for Diabetes vs. Nondiabetes (Framingham Study; Men and Women Ages 45–74 yr)

Relative risks	Factor of increased risk											
	Any CV disease		Mortality from CV dis.		Cardiac failure		Brain infarct		Coronary disease		Intermittent claudication	
	M	F	M	F	M	F	M	F	M	F	M	F
Unadjusted	2.5	3.7	2.6	7.2	2.8	7.7	3.3	5.6	1.9	3.6	4.7	8.9
Age adjusted	2.2	2.8	2.1	4.9	2.2	5.4	2.7	3.8	1.7	2.7	4.0	6.4
Risk factor adjusted*	2.1	2.0	1.7	3.3	1.8	3.8	2.2	2.2	1.7	2.1	4.2	5.0

Adjusted relative risk is calculated as exp, (B), where B is the estimated logistic coefficient of diabetes in a logistic function containing the additional factors listed.

* Adjusted for age, systolic BP, cigarettes/day, CHOL, ECG-LVH.

TABLE IX

International Collaborative Groups (Fifteen Populations)

Study	Oral Glucose (g)	Specimen Analyzed	Method of Analysis	Sampling Time
Australia	50	Venous plasma	Ferricyanide (AA)	1°
Denmark-40	1/kg	Venous serum	Glucose oxidase	F, 1°, 2°, 2½°
Denmark-50		Venous blood	Glucose oxidase	F
England	50	Cap. blood	Ferricyanide micromethod (AA)	2°
Finland-HP	75–90	Venous blood	o-Toluidine	F, 1°, 2°
Finland-SI	60–90	Venous plasma	Ferricyanide (AA)	1°
France	75	Venous serum	Ferricyanide (AA)	2°
Ireland	50	Venous serum	Glucose oxidase	1°
Italy		Venous plasma	Glucose oxidase	F
Japan	50	Venous serum	Glucose oxidase	1°
Scotland		Venous blood	Oxygen consumption	Casual
Switzerland	100	Cap. blood	Ferricyanide (AA)	F, 2°
U.S.-PG	50	Venous plasma	Hoffman (AA)	1°, Casual
U.S.-WE	100	Venous serum	Folin-Wu	2°
U.S.-CHA	50	Venous plasma	Hoffman (AA)	1°

available epidemiologic studies, then, give inconsistent results for serum glucose, at least as a single, cross-sectional measurement, as an independent risk factor for cardiovascular disease. Factors other than glucose alone, such as serum insulin levels, appear to be related to the increased cardiovascular disease in diabetics.

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Diabetes and Atherosclerosis in the Pima Indians

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Introduction

An extensive epidemiologic study concentrating on diabetes has been conducted for the past 15 years on the Pima Indians of Central Arizona. The Pima Indians are a relatively homogeneous population (1) who have resided in the area for about 2,000 years. They have the highest recorded prevalence of diabetes (2). The study population consists of over 4000 residents of the Gila River Indian Community who are of at least one half Pima heritage and are at least five-years old. They are examined at intervals of approximately two years. This examination includes anthropomorphic measurements, a glucose tolerance test, funduscopic examination, blood pressure measurements, renal function, tests and an electrocardiogram (EKG). Autopsy data have been collected when possible on subjects who died since 1965. This review summarizes some of the information obtained from the Pima population on the relation between diabetes and atherosclerotic cardiovascular disease (ASCVD).

Prevalence and characteristics of diabetes in the Pima Indians

The prevalence of diabetes mellitus in the Pima population (3) is shown in Figure 1. Diabetes was diagnosed when the 2-hour postload (75 gm) plasma glucose concentration was 200 mg/dl or greater either at a survey examination or in the course of routine medical care. The prevalence rates increased with age and were similar in both sexes up to age 44. Males reached a high of 40% in those 45–74 years old, while prevalence in females peaked at 68% in those 55–64 years old.

The incidence (that is, rate of development of new cases) of diabetes reached a maximum at 35–44 years of age in females and 45–54 years of age in males (Fig. 2). There were no known cases below ten years of age and only six with an onset before 20 years (4).

The Pimas are very obese, and the mean body mass indices (BMI) for both males and females exceeded those of the U.S. population at all ages (Fig. 3) (BMI = weight (kg)/height^2 (m^2). Percent "desirable" weight corresponds approximately to kg/m^2 × 4.39 for adult males and kg/m^2 × 4.76 for adult females (38).) Obesity is clearly a major factor in the high prevalence of diabetes (5). Figure 4 shows that the incidence of diabetes increased with increasing BMI. Obesity is also associated with hyperinsulinemia in this population (6). The development of diabetes seems to include the pattern of increasing weight (5), increasing insulin concentrations (7), and insulin resistance (8) associated with decreased glucose tolerance and disturbances in beta cell function (9).

Diabetes in the Pimas is noninsulin dependent (type II). Pima diabetics exhibit the classic symptoms of polydipsia, polyuria, and weight loss, and they have the usual complications of diabetes present in other populations. Diabetic retinopathy, defined as microaneurysms, hemorrhages, exudates or neovascularization in either eye as seen with a direct ophthalmoscope through dilated pupils, is present in 47% in diabetics with disease of at least 10-years duration (10). The incidence of retinopathy increases with duration of diabetes and is related to other indices of disease severity (11). Fifty percent of the diabetics with disease for 15 years or more have proteinuria (12). Moderate to severe diffuse glomerulosclerosis is seen in 65% of diabetics at autopsy (12). Further evidence of vascular changes has been obtained by measuring capillary basement membrane

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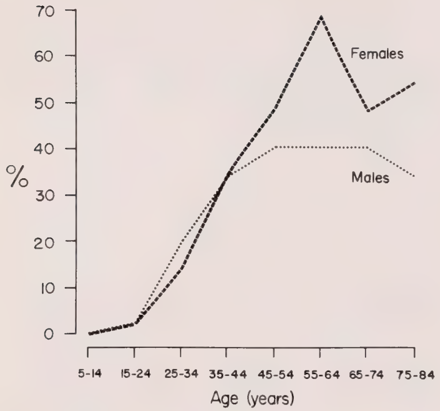

Fig. 1. Prevalence of diabetes in Pima Indians, ages 5–84. From Knowler et al (3).

thickness in muscle biopsies. Thickness is greater in diabetics and increases with duration of disease (13). The prevalence of diabetic pregnancies in the Pimas is ten to fifteen times that of the general population (2). Pregnancies complicated by diabetes are associated with a higher percentage of infants who are large for gestational age, and increased frequencies of toxemia, prematurity, congenital malformations, and perinatal mortality than are nondiabetic pregnancies (14).

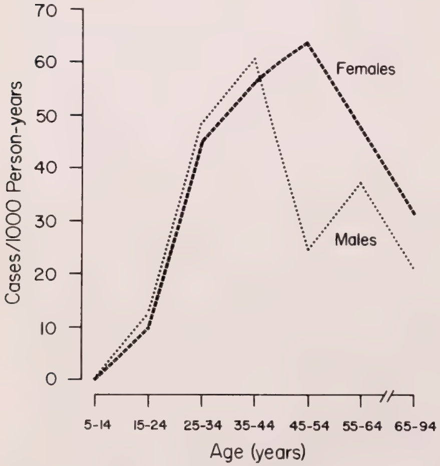

Fig. 2. Incidence of diabetes in Pima Indians, ages 5–94. From Knowler et al (3).

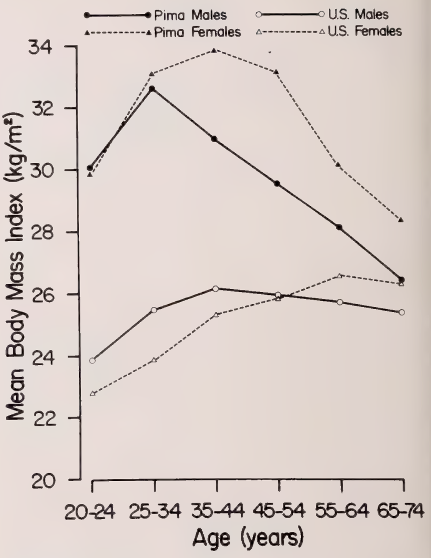

Fig. 3. Mean body mass index, i.e., weight/height^2 (kg/m^2), in Pima Indian adults, compared to measurements in the general U.S. population from the Health and Nutrition Examination Survey, 1971–1974 (Mr. Sidney Abraham, National Center for Health Statistics, personal communication). From Knowler et al (5).

In summary, the characteristics of the hyperglycemia and its complications in the Pima Indians are similar to those found in other Type II diabetics. Thus, because of the high frequency of diabetes, the Pimas are an excellent population for the study of the etiology and pathophysiology of this disease.

Relationship between diabetes and the risk of atherosclerotic heart disease (ASCVD) in the Pima Indians

The relationship between diabetes and ASCVD in this population has been examined (Table I) using data obtained from the standard 12-lead EKG at the biennial examination. EKG abnormalities were defined according to the Tecumseh criteria (15). In diabetic Pimas, the prevalence of EKG abnormalities was 2.1 times that of the nondiabetic Pimas. This observation was supported by determination of the frequency of cardiovascular disease (defined as sudden death with greater than 75% stenosis of at least one coronary artery, myocardial infarction, or stroke) among Pimas at

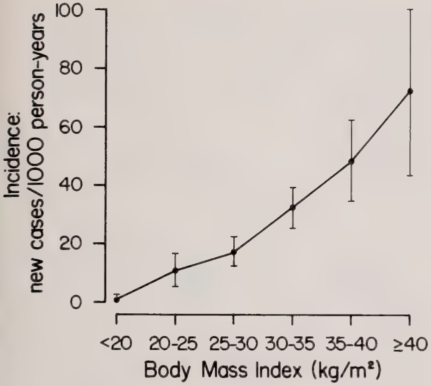

FIG. 4. Age-sex adjusted incidence rates (with 95% confidence intervals, i.e., ±1.96 standard errors) for diabetes in Pima Indians, by body mass index. From Knowler et al (5).

autopsy (Table II). This autopsy analysis was restricted to males who were at least 55 years old at death, because there was too little ASCVD to evaluate in females and younger males. The postload glucose concentration was determined at the last examination prior to death. Although the study was too small to be conclusive, cardiovascular disease was present 1.8 times as frequently in the diabetics; a prevalence ratio similar to that for EKG abnormalities shown in Table I.

The relationship between hyperglycemia and the development of ASCVD has been examined in a prospective study of 590 subjects at least 25 years old with normal EKGs at the initial examination as defined by the Tecumseh criteria (15). All subjects were reassessed for EKG abnormalities at a follow-up examination after six years (range 5−7 years). Age-sex adjusted six-year incidence rates of new EKG abnormalities are shown in Table III. EKG abnormalities occurred 1.7 times as frequently in diabetics as in nondiabetics. This was similar to the prevalence ratios for EKG abnormalities and cardiovascular disease at autopsy, but was in striking contrast to the greatly increased incidence of retinopathy in diabetics (16).

Several epidemiologic studies have documented an increased prevalence of ASCVD in diabetics (17, 18), but it is not clear which factor(s) in the diabetic state might be responsible. Recent studies by the International Collaborative Group (19) have attempted to examine the relationship between glucose levels and ASCVD in groups which excluded known diabetics. These studies showed no significant association between ASCVD and glucose concentrations, although there appeared to be an increase in ASCVD in subjects without known diabetes with the highest plasma glucose concentration. The data from the Pima population support these observations. The incidence and prevalence of ASCVD were higher in the diabetics as documented by increased EKG

TABLE I

Age-sex Adjusted[a] Prevalence of EKG Abnormalities[b] in Pima Diabetics and Nondiabetics 45−84 Years Old

Diabetic Status[c]	No. of Subjects	Rate ± SE (%)	Prevalence Ratio (Diabetics/Nondiabetics)	95% Confidence Interval for Ratio
Diabetic	541	11.7 ± 1.4	2.1	1.3−3.5
Nondiabetic	359	5.5 ± 1.3		

[a] Adjusted to 1970 U.S. White Population.

[b] EKG abnormalities are defined according to the Tecumseh Criteria (15).

[c] Diabetes was defined as 2 hr post load plasma glucose ⩾200 mg/dl at any examination.

TABLE II

Prevalence of Cardiovascular Disease[a] at Autopsy in Pima Diabetic and Nondiabetic Males at Least Age 55 Years at Death

Diabetic Status[b]	No. with ASCVD	No. of Subjects	Rate (%)	Prevalence Ratio (diabetics/nondiabetics)	95% Confidence Interval for Ratio
Diabetic	7	16	44	1.8	0.7−4.3
Nondiabetic	6	24	25		

[a] Cardiovascular disease was defined as sudden death with greater than 75% stenosis of at least one coronary artery, myocardial infarction, or stroke.

[b] Diabetes was defined as 2 hr plasma glucose ⩾200 mg/dl at the last examination preceding death.

TABLE III

Age-Sex Adjusted[a] Six Year Incidence of EKG Abnormalities in Pima Diabetics and Nondiabetics 45–74 Years Old

Diabetic Status[b]	No. of Subjects	Rate ± SE (%)	Incidence Ratio (diabetics/nondiabetics)	95% Confidence Interval for Ratio
Diabetic	162	8.2 ± 1.0	1.7	0.7–4.4
Nondiabetic	120	4.7 ± 1.3		

EKG abnormalities are defined according to the Tecumseh Criteria (15).

[a] Adjusted to 1970 U.S. White Population.

[b] Nondiabetic status defined as 2 hr glucose <200 mg/dl before and throughout the six year period.

abnormalities and cardiovascular disease at autopsy. Thus, even in this genetically homogeneous population with a lifestyle and lower propensity for cardiovascular disease (20, 21), diabetes was associated with an increased risk of ASCVD. However, the association between degree of hyperglycemia and the occurrence of EKG changes in the Pimas was not as marked as that seen between retinopathy and glucose concentrations (16). Thus other risk factors associated with diabetes must be examined for their relationship to macrovascular complications.

Relationship between plasma lipids and ASCVD in Pima diabetics

ASCVD in most populations appears to be associated with increases in total plasma cholesterol (22) and triglyceride (23) concentrations and with decreases in high density lipoprotein (HDL) (as recently reviewed by Heiss and Tyroler (24)). Quantification of risk factors in Caucasian populations has indicated that HDL cholesterol concentrations are better predictors of ASCVD than total cholesterol concentrations and that both are better predictors than triglyceride concentrations (25, 26). Since diabetes is associated with both elevated plasma lipid concentrations (26–32) and increased ASCVD (17, 18), it is important to establish how plasma lipids are related to ASCVD in diabetics.

Thirteen autopsy cases were identified with ASCVD as described above. Postmortem cases without evidence of ASCVD were matched for age (decade), sex, weight (within 5 kg), and diabetic status and treatment. Clinical characteristics for these subjects are shown in Table IV. Frozen serum was available which had been drawn from these individuals 1 to 11 years prior to death. HDL were isolated by the heparin-manganese precipitation method (33), and HDL and total cholesterol were determined on the autoanalyzer (34). Assays were standardized using reference material supplied by the CDC Lipid Standardization Laboratory (Atlanta, Georgia). Previous investigation of six healthy volunteers indicated that storage of frozen samples for up to one year did not affect plasma HDL concentrations (51.7 ± 11.2 mg/dl, mean ± SD vs 52.7 ± 11.6 after freezing, r = .99) and that up to ten freeze-thaws also had no significant influence on HDL concentrations (51.7 ± 11.2, mean ± SD vs 53.7 ± 10.9 after freezing, r = .99).

TABLE IV

Characteristics of Paired Subjects Studied at Autopsy

	NONDIABETICS		DIABETICS	
	WITH ASCVD[a]	WITHOUT ASCVD	WITH ASCVD	WITHOUT ASCVD
No. Males	5	5	5	5
No. Females	0	0	3	3
Age[b]	65 (48–79)	65 (46–85)	62 (37–73)	65 (36–83)
BMI[c]	23.9 ± 7.6[d]	24.3 ± 3.5	29.5 ± 1.8	28.5 ± 7.0
Therapy—				
Diet only			3	3
Oral hypoglycemics			3	3
Insulin			2	2

[a] ASCVD is defined as described in Table II. This analysis includes all autopsy data available on the Pima population (N = 220)

[b] mean (range)

[c] BMI refers to body mass index which equals weight (kg)/height^2(m^2)

[d] mean ± SEM

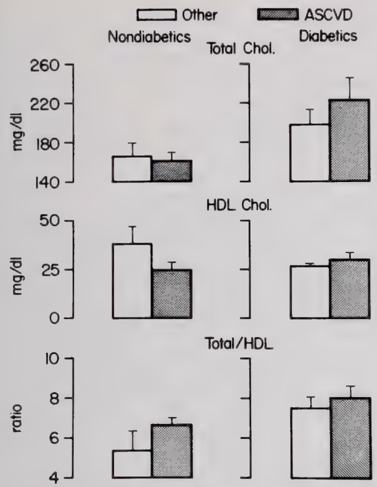

FIG. 5. Cardiovascular mortality and cholesterol levels in Pima diabetics and nondiabetics ▨ deaths from ASCVD; ☐ deaths from other causes matched for age, sex, weight and diabetes status and treatment values are mean ± S.E.M.

Figure 5 shows the total and HDL cholesterol concentrations in the specimens from subjects who subsequently were autopsied. There were no differences in total cholesterol, HDL cholesterol, or total/HDL cholesterol ratios between those dying with and without ASCVD. However, in nondiabetics, mean HDL cholesterol concentration tended to be lower in those with ASCVD and the ratio of total/HDL cholesterol was somewhat higher. In autopsied diabetics, the mean total cholesterol concentration was higher in those with ASCVD, but HDL levels in diabetics with evidence of ASCVD were similar to the HDL levels in those who died without ASCVD.

The relationship between plasma lipid concentrations and prevalence of EKG abnormalities was next examined using fresh plasma samples obtained from fasting patients seen at biennial examinations during a one-year period. Lipoproteins were isolated by ultracentrifugation (35) and total lipoprotein cholesterol and triglycerides were measured on the autoanalyzer (33, 36). EKG abnormalities were defined using the Tecumseh criteria (15). Subjects with abnormalities were matched with paired controls selected from those with no evidence of EKG abnormalities and matched for age (decade), sex, weight (within 5 kg), diabetic status and diabetic treatment (Table V). Lipid and lipoprotein data obtained on these four nondiabetic and ten diabetic pairs are shown in Figure 6. Statistical significance of differences in lipid variables between those with normal and abnormal EKGs was assessed with the paired t-test. In nondiabetics means for total cholesterol and total triglycerides were higher in those with abnormal EKGs, but the differences were not significant. HDL cholesterol levels and the ratio of total/HDL cholesterol were similar in nondiabetics with and without abnormal EKG's. In the diabetics, EKG abnormalities were associated with lower HDL cholesterol ($p < .05$) and higher ratios of total/HDL cholesterol ($p < .01$). Diabetic subjects with abnormalities had higher triglycerides but the difference was not significant.

Conclusions

Pimas are an interesting group for the examination of the relationship between arteriosclerotic heart disease and diabetes. The data ob-

TABLE V

Characteristics of Paired Subjects Analyzed for Relation Between EKG Abnormalities[a] and Plasma Lipoproteins

	Nondiabetics		Diabetics	
EKG STATUS	Abnormal	Normal	Abnormal	Normal
No. Males	0	0	4	4
No. Females	4	4	6	6
Age[b]	56 (51–72)	55 (46–68)	67 (57–78)	64 (53–78)
BMI[c]	29.8 ± 3.9[d]	31.4 ± 3.6	26.7 ± 2.1	25.2 ± 3.3
Therapy				
Diet		—	4	4
Oral hypoglycemics		—	4	4
Insulin		—	2	2

[a] EKG abnormalities were identified according to the Tecumseh Criteria (15).

[b] mean (range)

[c] BMI refers to body mass index which equals weight (Kg)/height^2 (m^2)

[d] mean ± SEM

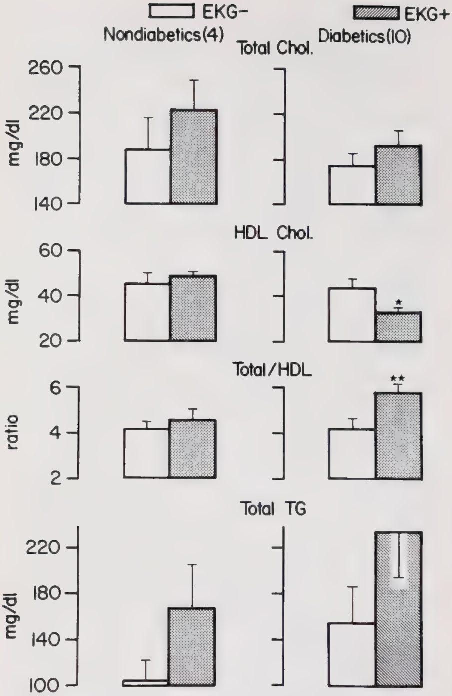

FIG. 6. EKG abnormalities and plasma lipids in Pima diabetics. ▨ EKG+ and ☐ EKG−. Diabetics are those with 2 hour plasma glucose ⩾ 200 mg/dl. EKG abnormalities are defined according to the Whitehall criteria (36). Data are shown for VLDL-TG. Data for total triglycerides are similar.

tained from repeated examinations of the members of this community over a 15-year period allow both longitudinal and cross sectional studies. In the Pimas, diabetes appears to be associated with increased ASCVD as evidenced by more EKG abnormalities and greater prevalence of ASCVD at autopsy. Thus diabetes appears to be a risk factor for ASCVD even though the population has a low background propensity for cardiovascular disease. However, the macrovascular disease was not as strongly related to hyperglycemia as was microvascular disease. Other aspects of the diabetic state may contribute to ASCVD. It will be necessary to examine factors such as insulin concentrations, blood pressure, mode of treatment, and duration of diabetes in this and other diabetic populations to assess their relation to ASCVD.

It has been previously demonstrated that diabetes is associated with increases in plasma triglycerides (27–29) and often with an increase in total cholesterol (31–32) and a decrease in HDL cholesterol (35, 37). We have begun to examine the relation between plasma lipid concentrations and ASCVD in the Pima diabetics to determine whether these are risk factors for the development of ASCVD as has been described in populations with a lower prevalence of diabetes (22–26).

Further studies are necessary to examine the relation between plasma lipids and ASCVD in diabetics. If ASCVD in diabetics is associated with high plasma triglycerides and cholesterol, then it may be important in the therapy of diabetes to control the plasma lipid elevations in an attempt to prevent the development of cardiovascular complications.

Acknowledgments

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Lipoproteins as Risk Factors for Vascular Disease in Diabetes

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Introduction

This symposium has been prompted by the need to review the problem of arteriosclerosis in Diabetes Mellitus. All agree that this is the major cause of morbidity in the adult with diabetes whether or not insulin treatment is required to maintain metabolic homeostasis (1). Although the well recognized risk factors (i.e., hypertension, elevated blood cholesterol and cigarette smoking) appear to be fully applicable to the diabetic population, other as yet unproven causes of arteriosclerosis must also operate since the incidence of coronary heart disease in diabetes is approximately two fold higher than one would predict using risk factor measurements (2). Less agreement exists on the issue of whether an increased prevalence of elevated risk factors is characteristic of diabetic populations. If one examines groups of diabetics who have gathered for treatment as in studies of university hospital diabetes clinics, a high prevalence of hypertension (3) and lipoprotein abnormalities (4, 5) may be found, whereas in a free living community, the risk factor status of diabetics is often much closer to the rest of the population (2).

This article focuses on the relationship of parameters of glucose control and obesity to plasma lipoprotein abnormalities among males and females with long standing insulin treated diabetes mellitus in a stable clinic setting. The data are drawn from the Mount Sinai Diabetes Clinic where over 400 insulin treated patients have been systematically studied over the past two years.

The Lipoproteins

Chylomicrons

The average adult consumes between 75 and 100 grams of fat each day and most of this is transported in the blood as chylomicron lipid. These are very large (100 nm) triglyceride rich particles which arise in the intestinal epithelial cell during fat absorption. They are cleared rapidly in normal subjects with a half life of 10–30 minutes. The peak level of chylomicrons occurs 3–5 hours after a meal and none should be detectable by routine analysis after 8–12 hours. Much of the phospholipid and protein that comprises the outer shell of the chylomicron is incorporated into HDL during the hydrolysis of the inner core of triglyceride by lipoprotein lipase, an enzyme found in muscle, adipose tissue and other extrahepatic tissues. The remaining components of the chylomicron are taken up by the liver and degraded.

Very Low Density Lipoproteins (VLDL)

VLDL (also known as pre beta lipoproteins) are produced primarily in the liver (85%–95%) and by the intestine (5%–15%) in the fasting state. These spherical particles (30–100 nM) are about 50%–75% triglyceride and the remainder is composed of approximately equal amounts of cholesterol, phospholipid and apoproteins. The lipoprotein lipase enzyme removes most of the triglyceride in peripheral tissues and portions of the phospholipid and proteins are transferred to HDL as with chylomicrons. The remaining remnant particles interact with the liver and may be taken up and degraded or may be further processed by a hepatic lipase and converted to low density lipoproteins.

Low Density Lipoproteins (LDL)

LDL arise primarily as the products of VLDL catabolism. These lipoproteins are thus smaller

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than VLDL (20−30 nM) having lost most of the triglyceride as above. They are, however, rich in cholesterol (50% by weight) with protein and phospholipid (25% each) also present. In humans, about 2/3 of the normal fasting blood cholesterol is present as LDL cholesterol. The slow clearance of this lipoprotein results in its circulating for days (half life 3 days). About 1/2 to 2/3 of these particles are cleared by specific cell surface receptors and about 1/2 to 1/3 by scavenger cells and nonspecific endocytosis. The liver is the major single organ of clearance, although most cells of the body have the LDL receptor on their surface. The number of these receptors is regulated by the cellular content of cholesterol.

High Density Lipoproteins (HDL)

These are the smallest (8−18 nM) of the lipoproteins in the four lipoprotein groups mentioned. Apoplipoproteins are their major constituent (45%−55%) with smaller quantities of cholesterol (20%−25%) and phospholipid (25%). HDL acts as a reservoir of specific apolipoproteins, providing these to newly synthesized chylomicrons and VLDL and accepting them in return when the triglyceride rich lipoproteins are degraded by the lipolytic enzymes (as above). HDL are also believed to be important in absorbing cholesterol from most tissues of the body and returning it to the liver where it can be excreted in the bile as bile acids or neutral steroids. Specific receptors for this purpose may exist in the liver.

Albumin–Fatty Acid Complex

Free fatty acids bound to serum albumin are a major source of energy for many tissues—particularly in the fasting state. One hundred to 200 grams of fat may be transported from adipose tissue each day by this route. This is the principal source of fat for VLDL synthesis in the liver and the source of organic acid ("ketone bodies") in diabetic acidosis. Insulin controls the output of free fatty acids by suppressing hormone sensitive lipase in adipose tissue.

Measuring The Lipoproteins

The availability of cholesterol and triglyceride determination as routine laboratory analyses provides the essentials for screeing for common lipoprotein elevations. Good autoanalyzers, quality control systems and standardization programs make it possible for routine laboratories to give excellent precision and accuracy in these lipid measurements. It is the lipoprotein cholesterol which appears to best predict risk (although measuring specific protein components may prove even more specific in the future). It is usually not satisfactory to perform electrophoresis on the plasma and to estimate the relative quantities of lipoproteins from the lipid staining bands. Electrophoretic mobility of lipoproteins is very sensitive to mishandling of the plasma and the staining process is highly variable. Analytic ultracentrifugation provides good quantitation of all lipoproteins, but requires expert attention to detail in the operation of very expensive equipment which can process few analyses per unit time.

The Lipid Research Clinic methodology is a compromise by which quantitative data on the major lipoproteins of interest (VLDL, LDL and HDL) are provided, yet large numbers of samples can be analyzed with good precision and accuracy (6). As a routine, the total plasma cholesterol (C) and total plasma triglyceride (TG) are analyzed by autoanalyzer using chemical or the newer enzymatic methods. The HDL cholesterol HDL_c is measured directly after precipitating all other lipoproteins using a divalent cation (e.g., Mn^{++} or Mg^{++}) with a polyvalent anion (e.g., heparin or dextran sulfate). If the triglyceride is below 500, the VLDL cholesterol can be estimated by dividing the total triglyceride by 5. The LDL cholesterol (LDL_c) is then estimated according to the following formula:

$$LDL_c = C - (TG/5 + HDL_c)$$

This formula assumes that there are no chylomicrons present and the VLDL are of normal composition. In dysbetalipoproteinemia (Type III hyperlipoproteinemia), the cholesterol content of VLDL is elevated relative to the triglyceride and the formula is not applicable. The presence of chylomicrons is easily determined by allowing the plasma to sit overnight and examining for a lipid layer floating at the top. When chylomicrons are present, or dysbetalipoproteinemia is suspected, the VLDL can be directly analyzed by one simple separation using the preparative ultracentrifuge. After exposure to 100,000× gravity for 16 hours, all VLDL is found at the top of an ultracentrifuge tube and the LDL and HDL are at the bottom (6). After removing these, the cholesterol and triglyceride in the VLDL can be measured. In dysbetalipoproteinemics, the ratio of triglyceride to cholesterol is usually between 2 and 3. When chylomicrons are present, this ratio is greater than 5 and may approach 20. After the ultracentrifugation, the LDL may be more directly determined by measuring the cholesterol in the bottom of the tube before and after precipitation with heparin/Mn or dextran sulfate/mg^{++} solutions.

Hyperlipoproteinemia

When the total cholesterol or triglyceride is elevated above the 95th percentile for age and sex, hyperlipoproteinemia is said to exist. Recent population studies have provided tables for this type of analysis. The blood sample must be drawn following 12 hours of no food intake and the subject should be on a diet characteristic of the population from which he is drawn. Declining body weight or the use of drugs affecting lipid metabolism may produce false negatives. This system has proven useful for defining populations in which lipoprotein elevations from major gene defects are very frequent. It has severe limitations when one wishes to compare different populations with differing socio-cultural features.

Using the above approach, the following "types of hyperlipoproteinemia" were defined by Fredrickson, Levy and Lees (7):

Type I	Chylomicrons are the predominant lipoprotein. VLDL is usually elevated a modest or moderate degree. The cholesterol is usually normal since LDL and HDL are reduced. This disorder is usually due to lipoprotein lipase deficiency or absence of a specific apolipoprotein activator for the lipase (apolipoprotein CII).
Type II	LDL are elevated. This may be due to a variety of causes including a defect in the specific cell surface receptor for LDL uptake. When the triglyceride is normal, the designation Type IIA is given. Type IIB is used when triglycerides are elevated due to increased pre beta migrating VLDL.
Type III	The VLDL have both beta and prebeta mobility on electrophoresis. The abnormal increase in the cholesterol content of VLDL has become a frequently used criterion. Both cholesterol and triglycerides are elevated. The disorder is usually due to a structural abnormality in apolipoprotein E resulting in an apparent defect in binding of partially degraded VLDL to the liver cell membrane. Deficiency of hepatic triglyceride lipase is a rare cause of Type III. LDL levels are usually low normal and HDL may be reduced.
Type IV	VLDL with prebeta mobility are increased. Hypertriglyceridemia with normal or elevated cholesterol results. Hepatic overproduction of VLDL appears to be the most common cause. Specific molecular defects have not been defined.
Type V	Both chylomicrons and VLDL are elevated. Overproduction of VLDL and a concomintant defect in clearance of triglycerides has been described as one etiology. No specific molecular mechanism is known.

All forms of hyperlipoproteinemia can result from primary genetic disorders. They may also be secondary to other disease processes. Uncontrolled diabetes may produce Type IV or V. Nephrosis, hypothyroidism, and liver disease are other common causes of Type II or Type IV.

Lipoproteins and Vascular Disease

Elevated total plasma cholesterol has been repeatedly shown to be a predictor of coronary heart disease, stroke and peripheral vascular disease. Since increased plasma cholesterol is usually due to LDL elevations, it was no surprise to find an even better fit of the risk curve with LDL cholesterol (8). Populations and nationalities that have a characteristic low risk of vascular disease also have low LDL levels (9). People with familial Type II hyperlipoproteinemia have early onset and high frequency of vascular disease complications. Monkeys and other animals in which LDL is elevated by diet, develop vascular lesions typical of human arteriosclerosis. Lowering LDL in animal models will often cause lesions to regress (10). There now seems little doubt that the LDL cholesterol is an important predictor of vascular events and can be a direct causative agent in arteriosclerosis. Some feel that with LDL cholesterol at or below 100 mg/dl, the vascular disease incidence in the Western "developed" nations would be reduced to that found in the less affluent parts of the world where LDL is already in this range (11). This is a concept worthy of much study, but yet to be proven.

Vascular disease prevalence and incidence falls as the HDL cholesterol rises. Plasma HDL levels are similar in male and female children, but drop 10 mg/dl at puberty in boys, remaining stable through adult life with average HDL cholesterol of about 45 mg/dl in men and 55 mg/dl in women. Individuals vary with levels ranging from 30−35 (5th percentile) to 75−85 (95th percentile) and over this 50 mg range of variation, tremendous changes in predicted vascular disease incidence were observed in several studies (8, 12). Very little information is available on methods of increasing HDL in normal subjects and no data demonstrating that a change in HDL will, in turn, produce a change in vascular disease incidence. Individuals with characteristics of sedentary life style, obesity, and cigarette smoking, tend to have the lowest levels. A negative correlation between triglyceride levels and HDL is also consistently found. Certain drugs such as progestational agents and beta blockers may reduce HDL; whereas estrogens, alcohol and nicotinic acid will increase this lipoprotein. It should be kept in mind that certain people with low HDL levels do not have increased vascular disease. The Pima Indians of the Southwestern United States is such a group (13). These people also have low LDL cholesterol. This data have led some to believe that HDL cholesterol is only important if the LDL cholesterol is elevated into the range seen in industralized Western man (125 to 200 mg/dl).

The relation of elevated triglycerides to coronary heart disease and stroke has been much more difficult to establish. In virtually all studies, triglycerides have some predictive power in a simple analysis (univariate analysis) of plasma levels and future vascular events. However, when one examines the correlation of elevated triglycerides with other risk factors (multivariate analysis), this predictive power of triglycerides may be explained by their close relationship with powerful independent risk factors such as reduced HDL cholesterol or increased LDL cholesterol (14).

In the study of families in which elevated VLDL is the only genetic marker, vascular disease does not appear with increased frequency. The same result is found in families with Type V hyperlipoproteinemia as a primary trait. Finally, autopsies of a few subjects with lipoprotein lipase deficiency in which chylomicron triglycerides have been at or near 1000 mg/dl for many years, have revealed no excess blood vessel disease. In certain lipoprotein abnormalities such as dysbetalipoproteinemia (Type III) and in disorders where both LDL and VLDL may be elevated, vascular disease does appear to be more frequent.

Materials and Methods

The Medical Diabetes Clinic at the Mount Sinai Medical Center provides full medical care for approximately 1250 adult diabetic patients at any time. The population examined for the present study was confined to those who were receiving insulin therapy and were on the Clinic roles as of September 1, 1979. Of the 750 patients meeting these criteria, 550 were located and interviewed. Over an eighteen month period, beginning on February 9, 1980, those completing this interview were invited by letter and phone call to return for a complete history and physical examination as well as a resting electrocardiogram. A fasting blood sample (12 hours) was obtained for lipids and lipoproteins, plasma glucose, hemoglobin A_{1c} (HbA_{1c}), complete blood count and other routine clinical chemical analyses. The urine was examined for protein and glucose by standard clinical methods. Patients who were not fasting were rescheduled for a later visit. Data sets from 410 patients were recorded and analyzed using the Statistical Analysis System (SAS) program in The City University of New York Computer Center.

Cholesterol and triglyceride levels were measured using enzymatic techniques with an ABA-100 Autoanalyzer (Abbott Laboratories). The HDL cholesterol was determined after precipitation of all other lipoproteins using $MgCl_2$/dextran sulfate (15). The LDL cholesterol was estimated by the method of Friedewald et al. (6). Cholesterol and triglyceride measurements in the lipoprotein laboratory at Mount Sinai and those in the Lipid Research Clinic laboratory were standardized by a third laboratory—the Lipid Standardization Laboratory, Center for Disease Control, Atlanta, Georgia. Exchange of samples with the University of California, San Diego Lipid Research Clinic Core Laboratory, confirmed that less than 5% difference existed in the mean cholesterol and triglyceride values obtained on 18 separate samples. The HDL cholesterol values by the method used at Mount Sinai were approximately 10% lower than those in the Lipid Research Clinic Laboratories. The values given in the Tables have not been adjusted for this difference. The LDL cholesterol was computed as: total cholesterol minus HDL cholesterol minus triglycerides divided by 5. Univariate Pearson correlation coefficients were computed for comparisons of variables were examined with a stepwise multiple regression procedure.

Only 9% of patients were categorized as having Type I diabetes by the criteria of experiencing ketoacidosis at least once and of having required insulin treatment beginning within one month of the diagnosis of diabetes. The remaining 91% were classified as Type II. The great majority of patients were Hispanic (46%) or black (41%). There were 286 (70%) women and 124 (30%) men.

TABLE I

Selected Characteristics of Study Patients

	Mean Values ± S.D. Total Cohort = 410	Female N = 286	Male N = 124	Units
1. Age	57.7 ± 12.9	57.7 ± 12.8	57.6 ± 13.4	years
2. Duration of DM	15.4 ± 9.2	15.2 ± 8.8	15.7 ± 9.9	years
3. Plasma Glucose	218.8 ± 95.9	223.8 ± 91.6	174.7 ± 87.1	mg/dl
4. Hgb A_{1c}	6.5 ± 2.1	6.8 ± 2.0	5.8 ± 2.0	%
5. Cholesterol	207.7 ± 47.4	212.7 ± 48.3	196.3 ± 47.6	mg/dl
6. Triglyceride	132.6 ± 72.6	138.7 ± 87.4	118.5 ± 68.3	mg/dl
7. HDL	45.1 ± 13.8	45.8 ± 13.0	43.6 ± 15.0	mg/dl
8. LDL	135.2 ± 42.9	139.5 ± 42.1	125.4 ± 43.3	mg/dl
9. Body Mass Index	30.6 ± 6.6	31.9 ± 6.9	27.7 ± 4.6	kg/m^2
10. Insulin Dose	0.69 ± 0.43	0.73 ± 0.47	0.61 ± 0.32	u/kg/day

TABLE II

Total Plasma Triglyceride (Females)

				Percentiles				
Age	Group	N	Mean ± S.D.	10th	25th	50th	75th	90th
49–49	Diabetic**	25	125 ± 100	41	52	95	147	171
	LRC*	648	105 ± 54	53	69	91	128	171
50–59	Diabetic	51	122 ± 63	60	82	102	155	218
	LRC	508	125 ± 65	62	78	107	154	216
60–69	Diabetic	70	150 ± 110	68	84	129	185	237
	LRC	275	134 ± 94	65	82	112	151	216
70+	Diabetic	51	141 ± 87	59	97	125	161	205
	LRC	143	128 ± 78	68	83	110	141	189

* Lipid Research Clinic Prevalence Study NIH Publication No. 80-1527, July, 1980.

** Diabetic Data–Mount Sinai Diabetes Clinic

Important general characteristics of the overall population are given in Table I. The 53 black and 49 Hispanic males for whom complete data were available, did not differ significantly in any of the characteristics listed. The Hispanic women had higher triglycerides and lower HDL cholesterol than the black women. Lipid and lipoproteins are given for all males and all females ages 40–79 by decade of life in Tables II through IX. All subjects who were younger or older than this age range as well as those with creatinine levels greater than 2 and proteinuria of 3 or 4+ by the Ames Dipstick test, were eliminated from the analysis. Patients receiving estrogen, corticosteroids or lipid lowering agents were also eliminated for comparison with the Lipid Research Clinic Prevalence Study values as in Tables II through IX. The Lipid Research Clinic study was conducted by a group of collaborating institutions using a standardized protocol in well defined target populations. These populations were diverse, located in ten different communities in the continental United States and Canada and included a broad range of geographic, socio-economic, occupational, age, sex and ethnic groups (16). The data were collected from 1972 to 1976.

Results

This cohort of diabetic women did not differ significantly from the men in age or duration of diabetes. However, as a group, glucose control was much better in the men (Table I) than in the women. The mean fasting plasma glucose of 175 mg/dl in the men was almost 50 mg lower ($p < 0.001$) than the mean level in women of 224 mg/dl. The mean hemoglobin A_{1c} of 5.8% in men was also significantly lower ($p < 0.001$) than this value for women (6.8%). These differences were found even though the mean daily dose of insulin in women was higher ($p < 0.01$) at 0.73 units/kg versus 0.61 units/kg in men. In part this may relate to the obesity evident in the women whose body mass index was 31.9 versus 27.7 kg/m^2 for men.

The total plasma triglycerides, total cholesterol and LDL cholesterol were significantly higher in women than in the men. The HDL cholesterol was not different in diabetic women and diabetic men.

TABLE III

Total Plasma Triglycerides (Males mg/dl)

Age	Group	N	Mean ± S.D.	Percentiles 10th	25th	50th	75th	90th
40–49	Diabetic**	10	92 ± 79	—	51	66	93	—
	LRC*	710	148 ± 121	67	89	121	170	235
50–59	Diabetic	16	140 ± 91	—	65	118	217	—
	LRC	601	144 ± 85	73	90	123	173	227
60–69	Diabetic	28	132 ± 79	62	78	101	153	261
	LRC	236	135 ± 107	63	81	110	157	210
70+	Diabetic	23	120 ± 57	61	87	106	159	206
	LRC	119	133 ± 79	71	87	115	152	202

* Lipid Research Clinic Prevalence Study NIH Publication No. 80-1527, July, 1980.

** Diabetic Data–Mount Sinai Diabetes Clinic

TABLE IV

Total Plasma Cholesterol (Females mg/dl)

Age	Group	N	Mean ± S.D.	Percentile 10th	25th	50th	75th	90th
40–49	Diabetic**	25	195 ± 39	140	168	196	223	243
	LRC*	644	202 ± 35	159	177	199	226	249
50–59	Diabetic	51	196 ± 39	146	163	203	224	254
	LRC	506	223 ± 38	176	195	222	240	273
60–69	Diabetic	70	220 ± 47	151	190	221	248	274
	LRC	275	233 ± 45	183	210	230	255	282
70+	Diabetic	51	223 ± 58	163	181	222	259	278
	LRC	143	225 ± 34	181	196	226	249	268

* Lipid Research Clinic Prevalence Study, NIH Publication No.80-1527, July, 1980

** Diabetic Data–Mount Sinai Diabetes Clinic

However, women in the diabetes clinic had reduced HDL levels when compared to the community based cohort of women (Table VIII) examined in the LRC study (16).

When one compares the plasma triglyceride levels by decade with the LRC population as is done in Tables II through IX, few differences are seen. Triglycerides are slightly higher in the diabetic women during the seventh and eighth decades. The LDL cholesterol values among female diabetics are not distinguishable from women in the community wide study. In the diabetic men, LDL is slightly lower in all decades except in the eighth. HDL levels are significantly lower among diabetic women (Table VIII). This is not corrected by adjusting for a maximum bias (minus 10%) in the methods used at Mount Sinai versus the LRC laboratories. This adjustment does remove differences between HDL in diabetic males and those in the LRC study (Table IX).

Significant correlations within the data set are shown in Tables X and XI. When each sex is examined separately, the total plasma cholesterol and the LDL cholesterol had no significant correlation with any parameter of glucose control. The triglyceride levels were positively correlated with fasting plasma glucose in both men and women, but with Body Mass Index, only in the men. A very strong negative correlation of HDL cholesterol with Body Mass Index and with plasma triglycerides was found in both men and women.

Discussion

To the clinician, the term Diabetic Hyperlipidemia, means markedly turbid plasma with triglyceride levels of several thousand mg/dl and Type V hyperlipoproteinemia. Such patients are usually not regular attendees of a diabetes clinic, but develop this condition while very negligent of their diabetic care or when severely ill as in ketoacidosis (17). Pre-existing hypertriglyceridemia on a genetic basis may underly these marked elevations that follow loss of glucose control (18). Insufficient insulin or severe insulin resistance leads to breakdown of triglyceride in adipose tissue with release of free fatty acids. When the free fatty acid flux increases in such a

TABLE V

Total Plasma Cholesterol (Males mg/dl)

Age	Group	N	Mean ± S.D.	Percentile 10th	25th	50th	75th	90th
40–49	Diabetic**	10	188 ± 50	—	149	170	215	—
	LRC*	710	209 ± 36	166	184	207	232	255
50–59	Diabetic	16	199 ± 54	—	171	185	215	—
	LRC	601	214 ± 35	170	189	213	237	262
60–69	Diabetic	28	202 ± 42	155	174	205	228	268
	LRC	236	219 ± 38	172	192	214	244	269
70+	Diabetic	23	204 ± 45	150	169	196	229	269
	LRC	119	210 ± 37	160	185	214	236	253

* Lipid Research Clinic Prevalence Study, NIH Publication No. 80-1527, July, 1980

** Diabetic Data–Mount Sinai Diabetes Clinic

TABLE VI

LDL Cholesterol (Females mg/dl)

Age	Group	N	Mean ± S.D.	Percentile 10th	25th	50th	75th	90th
40–49	Diabetic**	25	125 ± 34	84	98	119	144	170
	LRC*	644	127 ± 33	87	105	125	148	169
50–59	Diabetic	51	126 ± 33	80	99	127	154	168
	LRC	506	142 ± 37	96	116	140	164	193
60–69	Diabetic	70	145 ± 46	89	120	143	177	196
	LRC	275	153 ± 45	102	126	150	176	198
70+	Diabetic	51	150 ± 41	104	114	144	176	202
	LRC	143	149 ± 32	108	127	147	170	189

* Lipid Research Clinic Prevalence Study, NIH Publication No. 80-1527, July, 1980

** Diabetic Data–Mount Sinai Diabetes Clinic

patient, the production of VLDL becomes greatly accelerated. Clearance mechanisms involving lipoprotein lipase are insulin dependent as well, and thus, the removal rates of triglycerides are compromised and the lipemia grows steadily worse. As the condition deteriorates, VLDL production may begin to decline, but the addition of dietary fat as with a large meal, can flood the system with chylomicron triglyceride, sending the plasma levels to 5,000, 10,000 or even 20,000 mg/dl. Patients with such high levels frequently develop cutaneous eruptive xanthomata and hepatosplenomegaly due to fat filled macrophages in these organs. Pancreatitis may also develop in this situation and can lead to severe morbidity or death. Acutely, intravenous fluids, dietary fat restriction and intravenous insulin are usually indicated. For the long term, good glucose control and weight loss in the obese subject, usually brings the plasma triglyceride to more acceptable levels.

Mild to moderate hypertriglyceridemia is common in newly diagnosed diabetics and responds to treatment with insulin (19) and diet (20). Even those subjects who have quite normal triglyceride levels (i.e., less than 150 mg/dl) under treatment with conventional therapy, may show a significant reduction in fasting plasma triglycerides when very tight glucose control is achieved with tactics such as continuous subcutaneous insulin infusion (21). Given this consistent relationship between improving control and plasma triglycerides, it is surprising to find that the patients in the Mount Sinai clinic have a distribution of values so similar to the general population. The factors which militate against normal triglycerides were quite prevalent in the clinic population as reflected in a mean fasting plasma glucose of 210 mg/dl and a significantly elevated mean body mass index of 30.5. These factors were particularly evident in women whose mean fasting glucose level was 224 mg/dl and in whom the body mass index was 31.9 kg/m^2 as compared to 25 kg/m^2 for women of this age in the LRC study (16). The men had triglyceride levels below the age matched men in this general population study, even though there was an elevated mean fasting glucose of 175 mg/dl and slightly higher mean

TABLE VII
LDL Cholesterol (Males mg/dl)

Age	Group	N	Mean ± S.D.	Percentile				
				10th	25th	50th	75th	90th
40–49	Diabetic**	10	110 ± 42	—	80	103	141	—
	LRC*	710	140 ± 32	102	117	138	160	180
50–59	Diabetic	16	113 ± 41	—	91	119	135	—
	LRC	601	144 ± 33	103	121	144	165	188
60–69	Diabetic	28	132 ± 42	61	109	138	164	189
	LRC	236	148 ± 37	105	123	145	168	194
70+	Diabetic	23	139 ± 41	85	107	132	169	203
	LRC	119	142 ± 32	100	119	142	164	182

* Lipid Resarch Clinic Prevalence Study, NIH Publication No. 80-1527, July, 1980.
** Diabetic Data—Mount Sinai Diabetes Clinic

TABLE VIII
HDL Cholesterol (Females mg/dl)

Age	Group	N	Mean ± SD	Percentile				
				10th	25th	50th	75th	90th
40–49	Diabetic**	25	45 ± 15	33	35	42	47	74
	LRC*	644	58 ± 17	40	48	57	67	81
50–59	Diabetic	51	46 ± 13	30	37	44	52	61
	LRC	506	62 ± 17	41	50	61	72	85
60–69	Diabetic	70	46 ± 12	33	36	43	53	67
	LRC	275	64 ± 19	41	50	62	74	86
70+	Diabetic	51	46 ± 16	30	34	40	56	72
	LRC	143	61 ± 17	38	48	60	71	82

* Lipid Research Clinic Prevalence Study, NIH Publication No. 80-1527, July, 1980
** Diabetic Data—Mount Sinai Diabetes Clinic

body mass index of 27.7 kg/m^2 as compared to 26 kg/m^2 for men in the LRC population of this age range (16). Even though triglyceride levels were close to the normal distribution, fasting plasma glucose and number of urines positive (4+ by Clinitest) for glucose were strongly correlated with plasma triglycerides in both men and women. Excess body weight, as indicated by the body mass index, (wt/ht^2, kg/m^2) was also significantly related to the triglyceride level in both sexes.

In a study of 170 middle aged insulin treated diabetics in England, plasma triglycerides were not different from a control group selected from nondiabetic family members (22). Fasting blood glucose and relative body weight correlated with triglycerides in the Finnish diabetic men, but curiously, not in the women. In the only other report in which a control group has been compared to a similar patient population, 40 insulin treated diabetics (mean age 58.5 years) had significantly higher triglycerides (150 mg/dl vs 97 mg/dl). In Framingham, Massachusetts, when all diabetics, including those with severe glucose intolerance, were compared with the remaining population, the women, but not men, had slightly higher triglyceride levels (23).

The total plasma cholesterol is lower than expected for every decade of life (Table V) in both diabetic men and women in the Mount Sinai Clinic. This appears to be due to lower LDL cholesterol in the men and lower HDL cholesterol in the women. Since LDL cholesterol contributes approximately two thirds of the total plasma cholesterol, the two are highly correlated ($r = 0.88$). Additional cholesterol is carried in the very low density lipoproteins along with most of the plasma triglyceride. It is therefore not surprising that triglycerides correlate strongly ($r = 0.3$) with the total plasma cholesterol, but not with LDL cholesterol. There was no relationship between parameters of glucose control (HbA$_{1c}$ or fasting plasma glucose) and LDL cholesterol. Total cholesterol had a very weak ($r = 0.13$) correlation with HbA$_{1c}$, and this was not significant when analyzed in men or women separately. Finally, the correlations of the body mass index with LDL and total plasma cholesterol, were of marginal

TABLE IX

HDL Cholesterol (Males mg/dl)

				Percentile				
Age	Group	N	Mean ± S.D.	10th	25th	50th	75th	90th
40–49	Diabetic**	10	46 ± 20	—	35	43	52	—
	LRC*	710	45 ± 20	32	37	44	52	60
50–59	Diabetic	16	40 ± 13	—	29	36	52	—
	LRC	601	46 ± 13	31	37	45	53	61
60–69	Diabetic	28	44 ± 17	28	33	39	50	67
	LRC	236	51 ± 15	34	40	49	62	72
70+	Diabetic	23	40 ± 10	28	33	37	45	61
	LRC	119	51 ± 19	33	40	48	56	70

* Lipid Research Clinic Prevalence Study, NIH Publication No. 80-1527, July, 1980

** Diabetic Data–Mount Sinai Diabetes Clinic

TABLE X—A

Spearman Rank Correlation Coefficients for Lipids and Lipoproteins

	HbA_{1c}	FPG	BMI	Ins	Chol	TG	HDL
Female Diabetics (N = 286)							
Cholesterol	NS	NS	NS	NS	—	—	—
Triglyceride	NS	$r = 0.14$ $p = 0.03$	NS	NS	$r = 0.31$ $p = .0001$	—	—
HDL	NS	NS	$r = 0.22$ $p = 0.0003$	NS	NS	$r = .35$ $p < 0.0001$	— —
LDL	NS	NS	NS	NS	$r = 0.95$ $p < .0001$	NS	NS

TABLE X—B

	HbA_{1c}	FPG	BMI	Ins	Chol	TG	HDL
Male Diabetics (N = 124)							
Cholesterol	NS	NS	NS	NS	—	—	—
Triglyceride	NS	$r = 0.30$ $p = 0.0007$	$r = 0.28$ $p = .002$	NS	$r = 0.24$ $p = 0.007$	—	—
HDL	NS	NS	$r = 0.37$ $p < 0.0001$	NS	NS	$r = 0.77$ $p < 0.0001$	—
LDL	NS	NS	NS	NS	$r = 0.77$ $p < 0.0001$	NS	NS

Abbreviations used above are: HbA_{1c} = hemoglobin A_{1c}; FPG = Fasting plasma glucose; BMI = Body Mass Index; Ins = Daily dose of insulin in units per kilogram body weight; Chol = Plasma cholesterol; TG = Plasma triglyceride; HDL = High density lipoprotein; LDL = Low density lipoprotein.

significance in the total cohort. In the Finnish study, total plasma cholesterol and the LDL were not different from controls, but both increased with relative body weight. In Framingham, total cholesterol was also not different from normal in males or females. The lower values in the Mount Sinai Clinic may relate to dietary advice given many months or years before this survey. A dietary study is currently underway and data relevant to this issue should be available in the future.

It is quite apparent from Tables VIII and IX that the higher HDL cholesterol levels enjoyed by women in the general population, are not present in the diabetic women. The values for HDL in the diabetic men also appear lower than controls, but when corrected for the negative bias of −10% (4–5 mg/dl) inherent to our method for measuring HDL cholesterol, the values are virtually identical to those from the LRC population. A similar correction in the women would leave their HDL values lower than controls by approximately 10 mg/dl. These data agree with those from the Framingham study in which the diabetic women had low HDL cholesterol levels but not the men (23). This contrasts with the Helsinki experience in which HDL was higher than controls in both groups. In this latter study, HDL cholesterol had no significant relationship to relative body weight or glucose control. The failure to correlate with fasting glucose levels was also seen in the analysis of the Mount Sinai Clinic patients. This was unexpected, since several studies (24, 25), but not all (26), have found that whether the patients had low, normal or high HDL cholesterol values when initially examined, improved treatment with resulting lower plasma glucose and HbA_{1c} values led to increased HDL cholesterol. This raises the possibility that elevations in HDL with increased insulin may be only a transient phenomenon and these would therefore not appear in a cross sectional survey of a stable population. Another possibility is that uncontrolled dietary changes may have accompanied adjustments in the insulin regimen in some of these studies. A highly significant negative correlation of HDL cholesterol with body mass index (Table X), holds in the diabetic at Mount Sinai as in Framingham and in other studies of free living communities. The lack of a relationship of HDL with Percent Ideal Body Weight in the Helsinki clinics may have resulted from racial characteristics or may relate to the different method of measuring the prevalence of excess body fat. The other parameter in the present analysis which related significantly to HDL, was the plasma triglycerides ($r = 0.36$). This correlation has been a consistent finding in population studies.

Analysis of the lipoproteins in this clinic population gives no clues as to why the male diabetics may be at higher risk of arteriosclerotic cardiovascular disease. On the other hand, the levels of total cholesterol and of LDL cholesterol are much higher than those observed in populations where cardiovascular events are rare. Significant reductions in risk might be achieved by lowering these values. As a group, the women appear to have more ill effects than men. They are more obese, have higher blood sugars and higher triglyceride levels. Their HDL levels are lower than non diabetic women. Certainly, these factors may relate to the exaggerated increase in risk of vascular disease observed in diabetic women as compared to men.

It is hoped that reduced risk will follow reduction in blood sugar, LDL cholesterol and excess body fat. A study is currently underway in this population to determine if dietary change and better insulin management can be sustained for a prolonged period with additional supportive care by a nutritionist and nurse-educator. Significant reductions in cardiovascular risk factors as compared to those in a randomly selected control group of similar diabetics are the principal end points of this study.

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Hypertension as a Risk Factor in Diabetes Mellitus

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The incidence of essential hypertension in the general population is from 10% to 15% (1), whereas in the black population it is up to 30% (2). The chance, therefore, that on that basis any case of diabetes mellitus will be associated with essential hypertension is from about one in ten to one in seven in the general population and about one in three in blacks.

If diabetes mellitus is simplistically divided into insulin-dependent (early onset) (3) and insulin-independent (late onset) diabetes (4), the chance incidence in the former group rises because of the high risk of developing renal hypertension as produced by intercapillary glomerulosclerosis (5). This is not a renin-dependent hypertension (6) so that its cause is either salt and fluid retention, renoprival factors or small vessel systemic disease in general. If it is severe, it may be associated with proteinuria, hypoproteinemia and the nephrotic syndrome (7). The exact cause of the hypertension may vary from case to case or may be completely unknown. Because of the associated and therefore accelerated arteriosclerosis, renovascular hypertension is always a possibility, and this is usually renin-dependent (8). At any rate, the incidence of hypertension in the insulin-dependent group is increased from the previous figure to as high as 65% (9).

In the insulin-independent (late onset) group of diabetics, the patients are usually overweight (10) and this is a minor factor increasing the incidence of hypertension (11). Whether there are genetic factors that increase the association still further is unknown. Pyelonephritis (12) is a common complication of diabetes mellitus in both types and, when chronic, may produce some hypertension. To this may be added the chance occurrence of associated chronic glomerulonephritis.

What is the added risk when hypertension is associated with the insulin-dependent group? Here it is a very potent factor in accelerating renal insufficiency as well as atherosclerosis. It also increases the incidence of ischemic neuritis and myelitis (13) with their varied effects. In addition, diabetic retinitis is made worse and may result in amaurosis (14). These patients because of increased small, as well as large, artery pathology may succumb to uremia, myocardiopathy (15), or to myocardial infarction, heart failure, stroke or any other complication of atherosclerosis including aneurysm, peripheral thrombosis with intermittent claudication and/or gangrene.

In the insulin-independent (late onset) type of diabetes, the most common effect of the hypertension is to accelerate atherosclerosis. This may be partially attributable to abnormal serum lipid concentrations in hypertension (15a) which could contribute to increased risk in both types of diabetes mellitus. Obesity which may be associated with hypertriglyceridemia, hypercholesterolemia and increased low density lipoproteins (16) may also play a role here. It is also less common for these patients to succumb to renal insufficiency although it can occur if the hypertension itself becomes accelerated. In such an instance, the usual retinal and cerebral effects may appear. The most common increase in risk, however, results from such atherosclerotic complications as peripheral arterial thrombosis with or without gangrene, ischemic neuritis and/or myelitis and their protean manifestations, arteriosclerotic or dissecting aneurysm, stroke, myocardial infarction, heart failure, etc.

The clinician, however, must always keep in mind the fact that hypertension and hypergly-

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cemia may be manifestations of some rarer conditions such as pheochromocytoma (17), Cushing's syndrome (18) or acromegaly (19). If there are suspicious symptoms or signs associated with hypertension and hyperglycemia these rarer conditions should be ruled out since therapy is obviously different in such special endocrine syndromes.

As to therapy, the hypertension associated with diabetes of either the insulin-dependent or insulin-independent type should be treated if at all possible. Chronic pyuria and bacteriuria should always be looked for, diagnosed and treated appropriately. The antihypertensive drugs to be avoided if possible are the thiazide group which tend to aggravate the hyperglycemia (20), although, in either diabetic group this can often be met by increasing anti-diabetic medication. Clonidine, methyldopa, prazosin, reserpine, hydralazine and guanethidine can be used with caution and the beta blockers may be needed. A beta blocker like metoprolol or propranolol may mask the tachycardia of hypoglycemia in the insulin-dependent diabetic (21) and should be used with caution in late onset diabetes where these agents may increase hyperglycemia (22). Metoprolol, however, may not do this (23). Alpha inhibitors and blockers, as well as guanethidine and reserpine may increase the known tendency for the diabetic to have postural hypotension and syncope (24). Spironolactone may be useful as a diuretic unless kidney function is already compromised and the serum potassium is elevated (25). It is known, however, that hypertension in diabetes is not generally renin-aldosterone dependent (6) so that spironolactone may be expected to be less effective than usual.

All these antihypertensive drugs should, however, be avoided in certain diabetic complications such as severe renal insufficiency (26), intermittent claudication with or without gangrene (27 and stroke due to thrombosis (28); since lowering the blood pressure may make these conditions worse unless they are combined with other modalities of therapy. Good clinical judgement and careful follow-up is of the utmost importance in the evaluation and treatment of every patient with diabetes mellitus, especially if it is complicated by hypertension.

Summary

There is both an increased incidence as well as an increased risk when hypertension complicates either insulin-dependent or noninsulin-dependent diabetes mellitus. The increased risk is caused by increased small blood vessel involvement, particularly in the kidney and the heart, and by acceleration of atherosclerosis with all its complications. Antihypertensive therapy of certain kinds may also increase the risk if hypertension has complicated the diabetes. The association of hyperglycemia and hypertension may occasionally be part of special endocrine syndromes such as pheochromocytoma, Cushing's syndrome and acromegaly, any one of which requires special diagnosis and treatment.

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The Arterial Smooth Muscle Cell

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Studies of the atherosclerotic plaque date back at least one hundred years, when pathology was emerging as a major scientific discipline of medicine. Examination of the plaque by early pathologists revealed major features that quickly generated concepts about pathogenesis that still rebound in current theories. These features included thrombosis, cell injury and proliferation, lipid insudation and scar formation and calcification. With the current focus on cell biology and biochemistry, the terms have changed, the details are being refined, and the complexities grow, but the basic notions about pathogenesis are still discernible (1).

The vascular smooth muscle cell is remarkable for its range of capabilities during normal growth and development of the vascular tree. These capabilities are re-awakened in pathologic processes that show little of the architectural elegance or functional beauty that characterize the normal structure (2). The normal blood vessel wall is a marvel of structure-function integration, a fibrocellular network of enormous durability, strength and compact efficiency (3). The atherosclerotic plaque contains largely the same elements, but in a pattern of disarray, which alters vascular structure and function so severely as to compromise host survival.

The atherosclerotic plaque is characterized by smooth muscle cell proliferation, connective tissue deposition and lipid accumulation. Though macrophages constitute one cellular component of the complicated plaque, it is agreed that it is the smooth muscle cell that is largely responsible for the major features (4, 5). This review will deal with the proliferative, synthetic and other metabolic activities of this cell in atherogenesis and where appropriate, comment on the special aspects of diabetes that influence these activities.

Cell proliferation is a striking aspect of the response of the blood vessel wall to a variety of injuries, including those occurring during atherogenesis (2, 6). Loss of the endothelial surface lining layer itself or disruption of its normal functional properties leads to 1) adherence of platelets to the exposed wall matrix and 2) increased entrance of circulating macromolecules, including lipoproteins, into the environs of the underlying smooth muscle cells (7). This sets in motion a burst of smooth muscle cell (SMC) proliferation, migration of medial cells into the intima and the development of a muscle rich pad. The causes of this proliferation may include release of a protein from aggregated platelets that causes SMC proliferation (6), a direct stimulation of proliferation by high concentrations of low-density-lipoproteins (LDL) (8), immunologic injury (9) and perhaps hemodynamic forces acting on the wall of a localized vessel segment (10). The proliferative response of smooth muscle cells is also modulated by a variety of hormones; for example, estrogen greatly inhibits the response (2, 11) and growth hormone seems to augment it (12). Diabetic serum is also stimulatory; the specific component responsible is not known, though hyperlipemia per se, seems not to be the factor (8). High glucose and sorbitol levels in the media do not enhance proliferation of cultured smooth muscle cells (13), but their effects *in vivo* are not known. Insulin seems to slightly augment SMC proliferation *in vitro* and it has been proposed that increased circulating levels of insulin in adult-onset diabetics may aggravate this feature of atherosclerosis (14).

Connective tissue deposition is another major feature of the atherosclerotic plaque. This includes accumulation of collagen, elastin, and glycosaminoglycans (GAG). The role of this extracellular matrix in advancing plaque development is uncertain, though it has been postulated that lipid accumulation is enhanced in regions of

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excessive connective tissue deposition (2). Furthermore, it has been shown that certain GAG components, particularly dermatan sulfate, are highly charged and therefore may serve as potent binding sites for lipoprotein molecules that enter the wall (15). Recently, Fowler et al (16) have shown that in experimental atherosclerotic lesions of the primate, no more than 20% of the lipid deposition can be accounted for by intracellular deposits; presumably the remainder is present as extracellular pools. This question of the role of matrix in lipid deposition is not a trivial one; the therapeutic strategy needed against extracellular deposits would be drastically different from that addressed to intracellular metabolic processes. In any event, the extracellular connective tissue component is important in any consideration of atherogenesis in view of the clear evidence that it is one of the least reversible aspects of the atherosclerotic lesion (17).

In rats with experimental diabetes, the superimposition of hypertension results in marked potentiation of the increases in basement membrane thickenings of glomerular (18) and myocardial (19) microvasculatures seen in animals with diabetes alone. Hypertension is a potent promoter of connective tissue synthesis and deposition of blood vessels (2); effective treatment of hypertension may be one of the most salutary approaches to this feature of atherogenesis. The role of diabetes mellitus on this aspect of lesion development is not clear. Some have described considerable changes in the GAG profile (20); others have found little change (21), but newer techniques have not yet been systematically applied to the problem. In diabetic kidney tissue, certain glycosidases thought to be involved in normal basement membrane degradation have been shown to be markedly decreased from normal. Furthermore, treatment with insulin restores these enzyme levels to normal (22). These authors have speculated that the special vulnerability of renal tissue to glycoprotein deposition may reflect the combination of increased synthesis (23) and decreased degradation found in diabetics. In aortic tissue from animals with experimental diabetes mellitus, synthesis of basement membrane seems to be little changed from normal (Adamany and Wolinsky, unpublished observations), but lysosomal glycosidases are reduced and return to normal on treatment of the animal with insulin (24).

The third major feature of atherosclerosis, lipid accumulation, seems to reflect a summation of many abnormalities, the net result of which is an influx-efflux imbalance in vascular tissue and its cells. As we will see, diabetes mellitus worsens almost every component of this balance and therefore becomes more understandable as a risk factor for atherosclerosis and its clinical complications.

Hypercholesterolemia, specifically elevation of low density lipoprotein (LDL) levels, is a major risk factor for atherogenesis (25). Lest the problem be considered to be restricted to those with inordinately elevated levels of LDL or to those with genetic disorders, it should be remembered that at least two-thirds of all clinical sequelae occur in individuals with serum values within the 95th percentiles of serum cholesterol in the American population. Based on animal experimentation, this risk factor seems to act by promoting increased flux of LDL into the blood vessel wall. On the other hand, serum high density lipoprotein (HDL) levels are negatively associated with risk of cardiovascular disease. Though the mechanism of this protection is not certain, HDL has been shown *in vitro* to facilitate egress of cholesterol from overloaded cells (26); presumably, this lipoprotein class acts as a carrier for excess cholesterol back from peripheral tissues to liver for subsequent re-utilization or excretion into bile (27). In human diabetes mellitus, circulating LDL levels are clearly and directly related to the severity of the diabetes, whether based on fasting blood glucose or hemoglobin A_1 levels (28). The effects of glucose intolerance on plasma HDL levels on the other hand, are not so clearcut. Some report reduced HDL levels in human diabetics, even those with mild hyperglycemia (29), others note that HDL levels increase in direct relation to the degree of control of diabetes with insulin treatment (30). However, in all these studies, the potential confounding effect of obesity has not been accounted for. Obesity, which is so prevalent in diabetics, exerts an independent effect on HDL levels such that levels of this lipoprotein are reduced in the obese and rise in response to significant weight reduction (31).

In addition to these lipoprotein abnormalities associated with diabetes, the smooth muscle cells of the diabetic aorta show a distinct reduction in lysosomal specific activities of a variety of enzymes, including glycosidases and acid cholesteryl esterase (ACE), an enzyme involved in LDL catabolism (24). These findings of reduced ACE activity are not seen in either liver or kidney tissues of the diabetic animals; indeed, levels of this enzyme in these tissues are increased above normal (32). Given the relatively low levels of ACE in aortic tissue under normal conditions, it is striking that insulin deficiency further reduces the ACE level in the blood vessel wall in the face of increased circulating LDL levels, the presumed substrate for this enzyme. Insulin administration, however, restores enzyme levels to normal. Thus, a variety of changes–in circulating lipoproteins and vessel wall catabolic capacity—serve to worsen the influx-efflux lipid balance of the blood vessel wall of diabetics and may be one basis for their special predisposition to atherogenesis. In studies of human diabetics, recent evidence suggests that human monocytes also have reduced capacity for LDL catabolism and decreased ACE levels; insulin therapy stimulates these activities considerably (33).

Let us turn finally to a brief consideration of the interaction of other risk factors with diabetes mellitus in influencing the atherosclerotic process. Obesity has already been discussed in relation to decreased plasma HDL levels. Extremely common in the diabetic (as many as two-thirds of all diabetic women are obese), obesity also carries with it an increased prevalence of hypertension, hyperlipoproteinemia and worsening of glucose tolerance. Thus, the overweight patient offers a prime focus of intervention. Attention of the diabetologist to the carbohydrate content of his patient's diet should not obscure the need for a comprehensive dietary approach, that limits fat consumption and total caloric content as well.

Hypertension has been discussed with respect to its stimulatory effect on synthesis and deposition of extracellular connective tissue. In addition, however, increased blood pressure results in increased passage of intravascular protein molecules, including low-density lipoproteins, into the blood vessel wall (34). In the nonhypertensive diabetic, transvascular passage of circulating proteins is already increased over normal and can be restored toward normal by proper insulin treatment (34). Individuals who are both diabetic and hypertensive are thus particularly liable to suffer from exudative vascular complications. For example, a recent study showed a more than doubling of the incidence of exudative retinopathy in diabetics with systolic blood pressures over 145 mm Hg (35). In addition to these microvascular effects, hypertension probably increased the influx of lipid into the walls of larger blood vessels of the diabetic, thereby further worsening the influx-efflux relationship.

Exercise is a more controversial risk factor when one attempts to identify an independent effect on cardiovascular disease. However, a cautious program of exercise, dictated by the limits of the individual patient's status, can be recommended for associated beneficial effects. In addition to its positive influence on a patient's sense of well-being, exercise is useful as an adjunct in weight-reduction programs, is associated with a lowering of circulating LDL levels, an increase in HDL levels and seems to result in decreased resting systolic and diastolic blood pressure levels (36).

This overview has summarized major features of the activities of vascular smooth muscle cells in atherogenesis and has attempted to show some of the many mechanisms by which the problem is likely to be worsened when the individual is diabetic, as well. Furthermore, certain aspects of this potentiation are common to both macrovascular and microvascular diseases of the diabetic patient. In nearly every instance, insulin administration improves the functional or metabolic derangement to or toward normal. To be sure, we cannot yet offer the diabetic individual an optimal return to insulin-glucose homeostasis with presently available regimens. However, the demonstration of better metabolic control with systems of continuous insulin administration (37) and the more distant promise of islet transplantation provide the bases for a hopeful outlook. Even at present, enough information is at hand to adopt an aggressive approach to treatment; prevention of microvascular disease has been achieved in the experimental animal through early and carefully-adjusted insulin treatment (38). Although the variables in the clinical situation are less easily controlled, the clinician should be encouraged to embark with his patient on a program that emphasizes both optimal control of the diabetes and careful attention to common coexisting risk factors, with every expectation that, over the long term, some measure of benefit will be gained against the clinical ravages of vascular disease.

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Endothelial Cell Abnormalities

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As previously noted in this conference, the important long term effects of diabetes are primarily a consequence of vascular disease, either a microangiopathy involving the microcirculation, or atherosclerosis involving large blood vessels. Atherosclerosis is a change that involves musculoelastic arteries and large muscular arteries and leads to ischemic heart disease or sudden death, cerebrovascular disease, peripheral artery disease, and gangrene. These manifestations of ischemia may be expected when atherosclerosis narrows the lumens of large arteries such as coronary arteries to greater than 70% of their expected diameters. The hallmark of atherosclerosis is the fibrous plaque. These intimal thickenings or plaques are characterized by fibrocellular caps overlying deposits of extracellular and intracellular lipid. Such intimal fibrous plaques are believed to result from proliferation and migration of medial smooth muscle cells, increased deposition of connective tissue and accumulation of lipids primarily derived from the blood.

Experimental and clinicopathologic evidence indicate that arterial injury is the primary event in the pathogenesis of atherosclerosis (1–3). Injury and reactive changes in the wall are believed to predispose to the accumulation of blood borne lipid within the wall. In man, the selective involvement of particular arterial beds and the segmental distribution of atherosclerosis within certain portions of these arteries favor the concept that arterial injury may be important in the pathogenesis of atherosclerosis.

Recently, Ross and colleagues have attempted to formulate a unifying hypothesis to explain the role of various types of arterial injury in the pathogenesis of atherosclerosis (2). On the basis of a synthesis of evidence from both *in vivo* and *in vitro* experiments, they posit that the primary event resulting from mechanical, chemical, and immunologic injury is damage to the endothelium leading to endothelial desquamation. Endothelial desquamation results in loss of two of the important contributions of endothelium to the vessel wall, that is, the maintenance of the thromboresistant character of the luminal surface, and the barrier function of endothelium which regulates the transport of macromolecules into the arterial wall. Thus, following removal of the endothelium platelets adhere to the surface of the wall and release materials from their granules, including platelet derived growth factor released from the granule. This mitogen stimulates smooth muscle cells to proliferate, leading to intimal thickening. Macrophages may also interact with the injured wall and contain a mitogen for both smooth muscle cells and endothelial cells. Further, it is suggested that loss of barrier function may lead to increased transport of the cholesterol rich, low density lipoprotein into the wall and, if persistent, to intimal lipid accumulation.

Epidemiologic and clinicopathologic evidence indicate that diabetes mellitus accentuates atherosclerosis and its complications in coronary arteries, cerebral arteries and peripheral arteries. Although hyperlipoproteinemia, obesity, and hypertension are increased in diabetes, these changes are not generally believed to be of sufficient magnitude to account for the increased cardiovascular morbidity and mortality. This suggests that other events, perhaps arterial injury and/or changes in arterial wall metabolism, may be important in the pathogenesis of the degenerative disease in large vessels in the diabetic.

The question then arises as to whether or not the endothelial injury hypothesis will explain the increased incidence of atherosclerosis and its complications in diabetes? To the best of our

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knowledge, there is no direct evidence either in humans or experimental animals that endothelial injury is accentuated in diabetes or that it accounts for the enhanced atherosclerosis. There is some indirect evidence.

Thickening of the walls of capillary basement membranes is a characteristic finding in the microangiopathy commonly found in diabetics and also in some prediabetics (4). Based on evidence that fibroblasts of diabetic patients have a diminished life span in tissue culture, Vracko and Benditt suggested that there may be a hereditary somatic cell defect in diabetics in which cells may be especially susceptible to injury (5). Since various cells in the body are believed to be capable of only a finite number of divisions, an increased susceptibility to injury would limit the regenerative capacity in certain organs. In the instance of the pancreatic islets, added stress to beta cells in the diabetic may lead to injury with continued need for replacement of damaged cells. As a result of limited replication the population will be depleted more rapidly than in normals and insulin deficiency and diabetes will result. With regard to endothelial cells, these investigators suggest that the thickened and sometimes laminated basement membrane characteristic of the microangiopathy in the diabetic may be a manifestation of increased susceptibility of endothelial cells to injury with loss of these cells and regeneration. According to this concept, each new population of endothelial cells may be responsible for contributing a new layer to the thickened basement membrane.

It is also possible that there may be more subtle changes in endothelium. For example, insulin or a lack of insulin might have effects on endothelial function. Osterby and coworkers have demonstrated an effect of insulin on the function of endothelial cells in the rat with streptozotocin induced diabetes. These investigators noted a significant increase in the number of micropinocytotic vesicles in the endothelium of insulin treated diabetic rats. They suggest that a similar effect in man may be the morphologic counterpart of the clinically demonstrated decrease in plasma volume following injection of insulin (6). Similar endothelial injury in large vessels, if it occurs, may be important in the pathogenesis of atherosclerosis as suggested above. In this regard it is known that diabetic serum contains a growth factor for vascular smooth muscle cells. This growth factor is believed to have a growth hormone like activity (7).

Further indirect evidence of endothelial injury in the diabetic involves alterations of platelet function. Changes in platelet function have been described in diabetic patients as well as in experimental diabetes in laboratory animals. These changes include increased platelet adhesiveness (8), increased sensitivity to aggregation following stimulation by epinephrine, collagen and arachidonic acid (9), increase platelet turnover (10), increased release of platelet factor 4 (11), increased activity of prostaglandin synthetase system as evidenced by the synthesis of increased quantities of PGE-like substances (12), thromboxane and decreased synthesis of prostacyclin (12−15) and von Willebrand factor (16). Several of these findings can be interpreted to suggest that endothelial injury has stimulated platelet interaction with the focally damaged or denuded endothelial surface.

In general, there are many problems with interpretation of data concerning platelet alterations. Several of the findings have proven difficult to repeat. The reasons for this are not entirely clear but differences in the patient populations studied may be important. Further, the significance of the findings is often difficult to interpret. Some studies have involved patients with overt manifestations of vascular disease such as coronary artery disease. Under these circumstances, changes in platelet function could represent: 1) reaction with ulcerated fibrous plaques characteristic of advanced atherosclerosis, 2) an expression of metabolic perturbations in diabetes on platelet function, 3) a reaction of platelets with damaged arterial wall at sites of lesion initiation, or some combination of these. In other studies, patients without overt vascular disease were selected (17). However, even in these instances alterations of platelet function may be indicative of platelet reaction with already established atherosclerosis and not with damaged endothelium involved in lesion initiation. As most experienced pathologists know, atherosclerosis begins early in life and by the time of early adult years has usually reached moderately extensive change in many individuals, especially males, even though they may have no overt manifestations of disease. However, studies in animals do suggest that experimentally induced diabetes may have effects on platelet function before induction of arterial disease (18).

Although a role for endothelial injury has not been established in the pathogenesis of the accentuated atherosclerosis seen in the diabetic, there is, as noted above, some indirect evidence to suggest that endothelial injury may be important. What etiologic factors may be important in this injury and how do they lead to injury and atherosclerosis? Clearly the answers to these questions are not known. However, a consideration of the pathogenesis of injury induced atherosclerosis may be useful for future experimental inquiry. For this purpose we have chosen two model systems in which biologically significant forms of arterial injury have been used, one involving immunologic arterial injury and the other a model of viral induced atherosclerosis that has recently been shown to be a significant injury component. These two models may be especially pertinent for consideration in relation to diabetes. Epidemiologic and experimental evidence suggests that infection with picornaviruses may be important in the pathogenesis of some cases of insulin dependent or juvenile diabetes in humans as well as diabetes in experimental animals (19, 20). Immunologic reactions may also be important. Immunogenetic factors have been implicated in the response to the virus infection that may lead to this type of diabetes (21). In humans, insulin dependent or juvenile onset diabetics have been shown to have autoantibodies and sensitized lymphocytes directed against beta cells (22, 23). Further, the immune response has been shown to be important in the genesis of this type of diabetes in experimental animals. It has also been suggested that immunologic phenomenon may be important in the accentuated atherosclerosis seen in diabetes (24, 25).

There is considerable clinicopathologic evidence to implicate immunologic injury in the accelerated atherosclerosis associated with other disease processes. For example, some patients with rheumatic disease, lupus erythematosus, and rheumatoid arthritis have been shown to develop precocious atherosclerosis (26–29). Rapidly progressive atherosclerosis also has been found to be one of the most important long term complications of graft rejection (30). In addition, a number of virus infections have been implicated in vascular disease both in man and in experimental animals (31). In this connection, hepatitis B virus has been implicated in arteritis and arteriosclerosis in humans and human herpes-viruses have been shown to proliferate in human endothelial cells in culture and to modify many of their characteristics (32–34). Coxsackie virus infections have been implicated in endothelial injury and atherosclerosis in man (35). Arterial disease associated with lupus erythematosus, hepatitis virus and rheumatoid arthritis is believed to be mediated by immune complex induced injury while that resulting from some other virus infections and graft rejection may be a result of cell-mediated immune injury.

In addition to this clinicopathologic data, there is experimental evidence to implicate immunologically and viral-induced arterial injury in the pathogenesis of atherosclerosis. Experiments from this laboratory indicate that the synergy of diet induced hyperlipemia and immunologically induced vascular injury can lead to atherosclerosis (36). Arterial injury was induced in rabbits by repeated intravenous injection of foreign serum protein approximately every four to eight weeks and hyperlipemia resulted from feeding a cholesterol-poor, lipid-rich diet for as long as 17 months. Feeding this diet resulted in elevation of serum cholesterol concentrations from the normal range of 40–80 mg/dl to between 150 and 400 mg/dl, comparable to that of adult humans in developed Western countries. In some rabbits, changes developed in arteries which bore striking resemblance to those of chronic human atherosclerosis, both with regard to morphologic characteristics and distribution in the arterial tree (Figs. 1, 2). These experiments confirm the results of earlier experiments in which rabbits were fed a cholesterol supplemented diet and subjected to immunologic challenge over a short period of time resulting in less chronic lesions resembling some stages of human atherosclerosis (37). In both of the experiments discussed above, lesions resulting from diet induced hyperlipemia alone were different in both morphology and distribution from those induced by the synergy of hyperlipemia and immunologic injury and did not resemble atherosclerosis in man.

In subsequent experiments, sites of immunologically induced injury were allowed to heal for 40 to 80 days prior to the induction of hypercholesterolemia. It was observed that lipid accumulation occurred preferentially at sites of intimal thickening, that is, sites of previous injury (Figs. 3, 4). These experiments indicate that in rabbits sites of intimal thickening, resembling diffuse intimal thickening in human arteries, have increased avidity for lipid for at least several weeks or months after the initiating injury (38). Findings suggest that, in man, sites of intimal thickening, perhaps representing the cumulative effect of arterial injury induced months or even years previously, may preferentially accumulate lipid and evolve as atherosclerosis later in life when plasma lipids increase.

It is important to emphasize that in these experiments coronary arteries were especially susceptible to lesion development, along with the

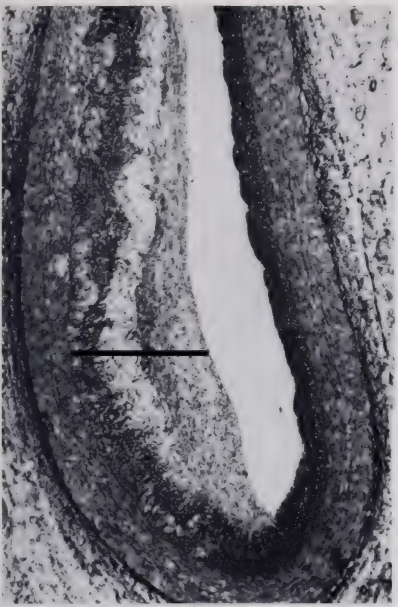


FIG. 1. Atherosclerosis of the right coronary artery of a 35 year old man with marked coronary atherosclerosis, old and recent myocardial infarcts, and aortic and mitral stenosis. Lumen of artery is narrowed by musculoelastic intimal thickening characterized by fatty-proliferative changes with pooling of lipid and very little elastic tissue. (Intima identified by bar). Note similar changes in the rabbit atherosclerosis shown in Figure (2) (Weigert-hematoxylin and eosin, ×25 (From Minick and Murphy (36) with permission of the American Journal of Pathology).

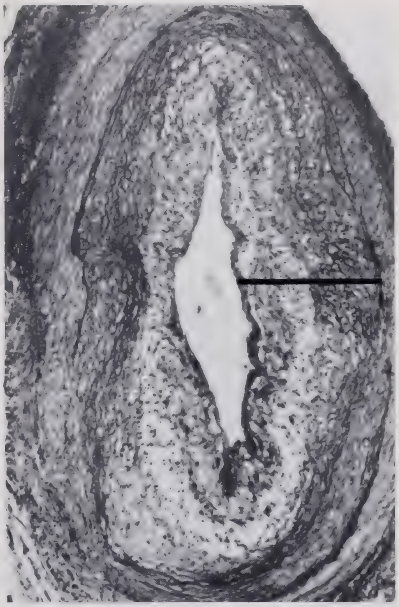


FIG. 2. Atherosclerosis of the right coronary artery of rabbit that received semisynthetic lipid-rich diet and 7 injections of horse serum over a period of 9 months. Average total cholesterol in serum, 157 mg%. Atheromatous intimal thickening with straightening, fragmentation, and reduplication of internal elastic membrane (intima identified by bar). Fatty-proliferative changes with very little elastic tissue overlie a layer of musculoelastic intimal thickening. Note marked similarity to the human atherosclerosis shown in Figure (1). The atheromatous change seen here did not occur in coronary arteries of control rabbits that received semisynthetic lipid-rich diets without injections of foreign serum protein (Weigert-hematoxylin and eosin, ×75). (From Minick and Murphy (36) with permission of the American Journal of Pathology).

aorta, and some major system arteries. Cerebral arteries were spared. This observation indicates differential vulnerability of various vascular beds to specific injuries and may bear on the preferential involvement of certain arterial beds with arteriosclerosis, the earlier occurrence of manifestations of ischemic heart disease than arteriosclerotic brain disease and the increased involvement of peripheral arteries in diabetics.

It has recently been demonstrated that vascular injury mediated by immune complex disease may also act synergistically with hyperlipemia to enhance diet-induced atherosclerosis in nonhuman primates. In initial experiments, vasectomized monkeys with circulating immune complexes consisting of sperm derived antigens and antibodies thereto, were observed to develop significantly accentuated atherosclerosis as compared to sham operated controls (39). In subsequent experiments, it was shown that vasectomy resulted in accentuated atherosclerosis even in monkeys fed monkey-chow diet which is low in lipid (40).

Clinicopathologic observation and results of experiments also indicate that immunologically induced vascular injury leading to atherosclerosis can be mediated at least in part by cellular immune mechanisms. This has been observed clinically in the unexpectedly severe and rapidly developing atherosclerosis found to occur in some human cardiac homografts (41). Coronary athero-

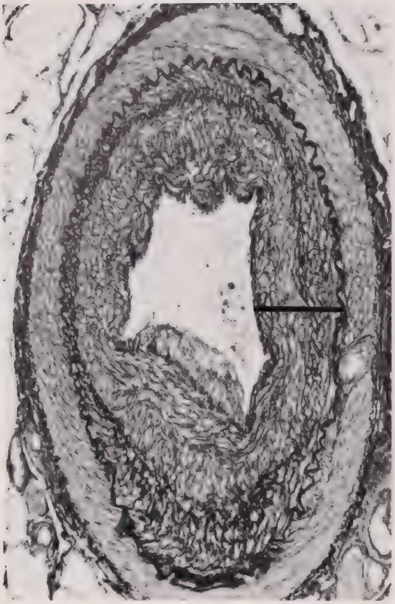


FIG. 3. Lumen of rabbit mesenteric artery is narrowed by musculoelastic intimal thickening (bar) resembling diffuse intimal thickening in man. Arterial change characteristic of those seen in rabbits fed diets low in lipid injected with foreign serum protein and sacrificed 40 to 80 days after the last injection (Weigert-hematoxylin and eosin, ×95). (From Hardin NJ, *et al* (38) with permission of the American Journal of Pathology.

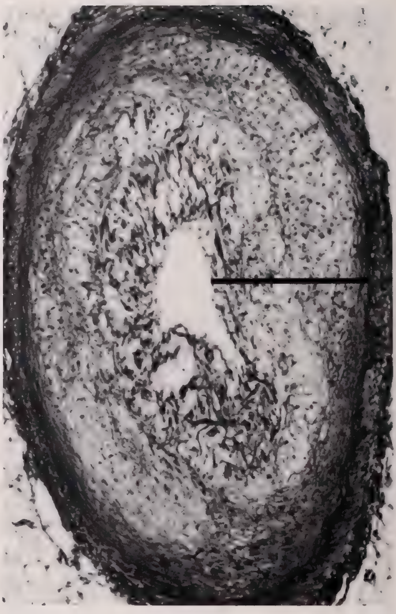


FIG. 4. Atherosclerosis of rabbit artery representative of that induced in rabbits repeatedly injected with foreign serum protein and subsequently fed cholesterol-supplemented diet 40 to 80 days after last injection. Morphologic and statistical evidence indicates that areas of injury-induced fibromuscular intimal thickening (bar) like those illustrated in Figure 3 preferentially accumulated lipid and evolved as atherosclerosis like that illustrated in this artery (H & E ×60). (From Hardin NJ *et al* (38) with permission of the American Journal of Pathology).

sclerosis in association with graft rejection has also been investigated in experimental animals. In our laboratories, cardiac homotransplants were performed in the necks of 60 rabbits. Diet-induced hyperlipemia led to atherosclerosis in the aorta, coronary arteries, and cardiac valves of transplanted hearts that were not seen in the recipient rabbits' own hearts (Figs. 5, 6). Atherosclerotic lesions were also found in lesser numbers in arteries in hearts transplanted in rabbits that received no lipid supplement and had only slightly elevated serum cholesterol concentrations (42).

Since the atherosclerosis induced by immunologic injury resulting from immune complex disease and graft rejection so closely resembled human atherosclerosis, it appeared particularly appropriate to investigate the early changes in these lesions in an attempt to learn more about their pathogenesis. Results of ultrastructural studies with the use of transmission and scanning electron microscopy indicated that endothelial injury with desquamation was an early component of the arterial lesions in both of these models (Fig. 7) (43, 44). The presence of endothelial denudation suggests that reaction of platelets with the denuded endothelial surface may be an important component of these lesions. Support for the role of platelets in the pathogenesis of arteriosclerosis comes from experiments in which investigators tested the effect of alteration of platelet function. In the instance of graft induced arterial injury, it has been recently shown that arteriosclerosis can be completely inhibited with such a pharmacologic agent, dipyridamole.

Cellular immune mechanisms may also be involved in the development of atherosclerosis associated with viral infection. It has been recently

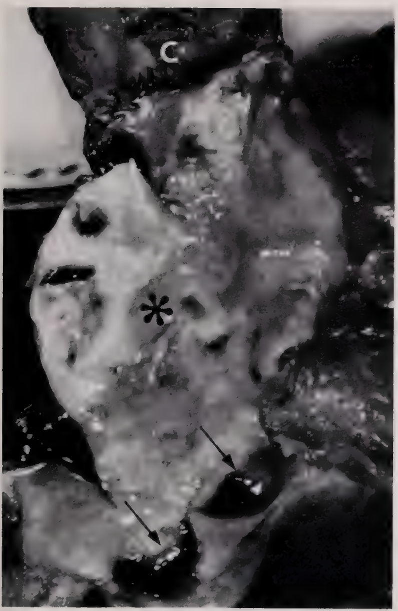


FIG. 5. Cardiac allograft and recipient's heart and aorta from rabbit fed a cholesterol-supplemented diet and treated with immunosuppressives. Rabbit was sacrificed 92 days after transplantation. Note marked atherosclerosis of transplanted aortic valve (arrows) and ascending aorta (*). Atherosclerotic change ends abruptly at line of anastomosis with recipients common carotid artery (c). (From Alonso DR *et al* (42), with permission of the American Journal of Pathology).

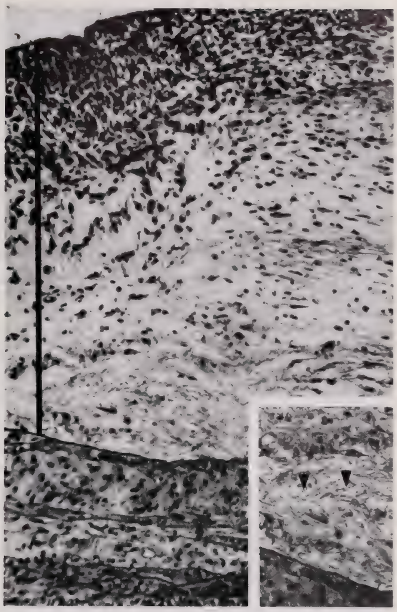


FIG. 6. Proximal left main coronary artery of cardiac allograft that functioned for approximately two weeks. The lumen is markedly narrowed by atheromatous intimal thickening (bar). Cellular cap covers lipid deposits deep in intima. Recipient rabbit was fed cholesterol-supplemented diet and received no immunosuppressive agents (Weigert—H & E ×45). (From Alonso DR *et al* (42), with permission of the American Journal of Pathology).

INSET. Serial section of artery illustrated in Figure 6. Atheromatous gruel containing cholesterol clefts (arrowheads) is present deep in intima (Weigert—H & E, ×143). (From Alonso DR *et al* (42), with permission of the American Journal of Pathology).

demonstrated that infection of genetically appropriate strains of specific-pathogen-free chickens with Marek's disease herpesvirus will lead to occlusive atherosclerosis (Figs. 8–11), (45, 46). Arterial lesions in these chickens were remarkable for several reasons. Even though the lesions were induced in a period of seven months, they bore striking resemblance to chronic human atherosclerosis. Further, lipid-containing chronic atheroscerotic lesions were induced in chickens fed relatively lipid-poor commercial chicken ration that had normal serum cholesterol concentrations. Modest hypercholesterolemia, of a magnitude similar to that seen in Western man, increased the incidence of chickens with arterial lesions and accentuated the number of arterial lesions as well as the severity of the arteriosclerotic change. Thus, in these chickens at least one other risk factor acts synergistically with virus infection to accentuate the severity of disease. If herpesviruses were shown to induce similar arterial changes in man, one would anticipate all populations to have arteriosclerosis, and that the atherosclerosis would show a striking increase in severity in population with other risk factors, for ex. hypercholesterolemia.

In other preliminary experiments, we have demonstrated that the arterial lesion in this model is associated with the presence of viral antigen, infiltration by lymphocytes, and small foci of necrosis within the media of the arterial wall. Infection with Turkey herpesvirus has been shown to protect from infection with the Marek's disease herpesvirus (47, 48).

The precise mechanism of arterial injury in

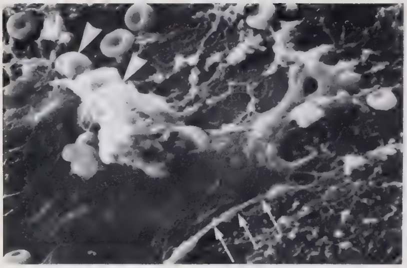
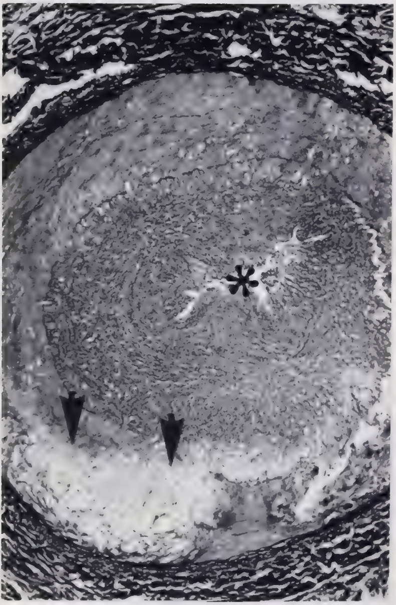


FIG. 7. Photomicrograph of endothelial surface of rabbit that received one injection of horse serum and was sacrificed 15 days later. Endothelium is partially denuded and red cells and platelets adhere to the surface (arrowheads). Note rolled edge of endothelial cell where it is separating from the aortic surface (arrows) ×1290. Similar endothelial denudation was seen on the luminal surface of coronary arteries following transplantation. (Minick *et al* (43) with permission of Thrombosis and Haemostasis).



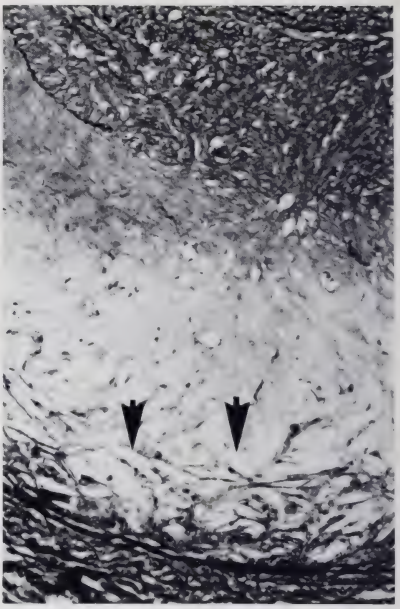


FIG. 9. Higher magnification of artery shown in Figure 7. Note foam cells, extracellular lipid, and cholesterol clefts (arrowheads) in media (Weigert-van Gieson ×190). (From Fabricant CG, *et al* (45) with permission of the Journal of Experimental Medicine).

FIG. 8. Atheromatous change in gastric artery of *normocholesterolemic* chicken infected with Marek's disease herpesvirus and fed a diet low in cholesterol. Lumen (*) is occluded by thickened intima. Atheromatous change is present deep in intima and media (arrowheads). (Weigert-van Gieson ×40). (From Minick *et al* (46) with permission of the American Journal of Pathology).

serum sickness and graft rejection is not known. However, there is a considerable amount of information, much of it recently obtained. It is known that immune complexes in slight antigen excess are necessary for the induction of arterial necrosis (49). In rabbits, deposition of immune complexes and vasculitis is inhibited by depletion of platelets or administration of drugs that block histamine or serotonin (50). Complement and leukocytes are also necessary for the development of the arterial lesions. The stimulation of release of histamine and serotonin from rabbit leukocytes and platelets is mediated by complement or the interaction of antigen with IgE bound to the surface of basophils. These cells release histamine and also platelet activating factor, now known as acetyl glyceryl ether phosphyorylcholine, which causes platelets to transiently aggregate and to release vasoactive amines (51–53). PAF also causes transient loss of platelets and leukocytes from the blood and accumulation of platelets at

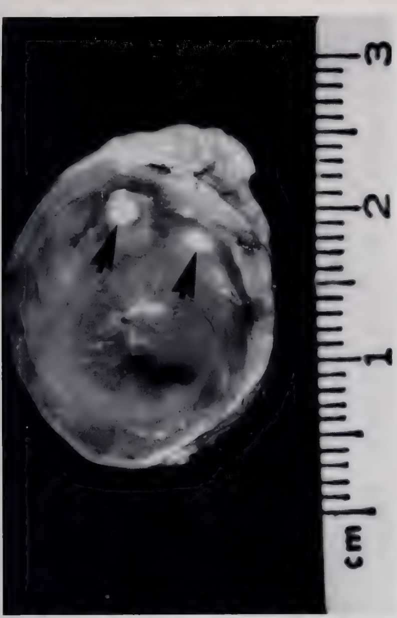


FIG. 10. Cross-section of heart of a chicken infected with Marek's disease herpesvirus (MDV) and fed cholesterol-supplemented diet for 15 weeks. The lumens of major coronary arteries are occluded by atherosclerotic change as seen in the two arteries in the upper portion of this photograph (arrowheads) (×2). (From Minick *et al* (46) with permission of the American Journal of Pathology).

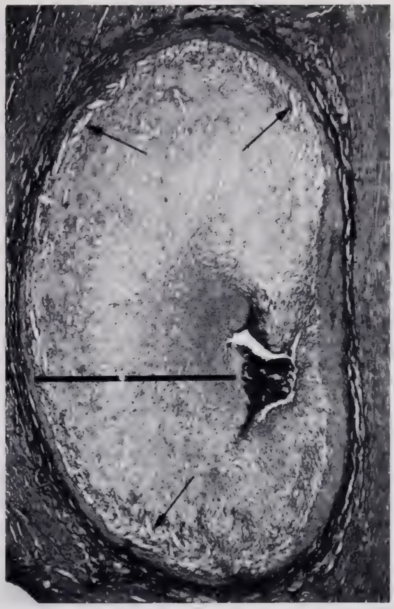


FIG. 11. Major coronary artery of chicken infected with MDV and fed a cholesterol-supplemented diet for 15 weeks. Cholesterol clefts (arrows) are present in atheromatous intima (bar) adjacent to the media. The subjacent media is markedly thinned. There is no cellular reaction in adventitia and little adventitial thickening (Weigert van-Gieson ×30). (From Minick *et al* (46) with permission of the American Journal of Pathology).

the site of immune complexes (54). In addition, challenge of sensitized basophils results in the release of enzymes capable of clearing and activating prekalikrein or Fletcher factor, which in turn, can initiate activation of the intrinsic pathway of coagulation leading to clot formation, fibrinolysis, and the generation of bradykinin, thus potentiating the inflammatory response vessel permeability (55, 56).

It is believed that release of histamine and serotonin from basophils and platelets leads to increased endothelial permeability as a result of endothelial contraction. This allows large macromolecules such as immune complexes to gain access to the arterial wall. Activation of complement within the wall is chemotactic to neutrophils and macrophages (57, 58). In turn, liberation of various hydrolases from neutrophils, macrophages and platelets leads to damage to the wall, including endothelial cells, perhaps resulting in endothelial denudation. It should be pointed out that this hypothetical sequence is dependent on the concept that endothelial cells in large arteries contracts in response to vasoactive amines like those in venular endothelium (59). Although there is some evidence to suggest that such contraction occurs, it has not been proven (60). However, it has been shown that large vessel endothelial cells contain contractile proteins (61).

The surface of endothelial cells themselves may play a role in localization of immune complexes and in this manner influence endothelial and other aspects of arterial injury. There is some disagreement as to whether normal endothelial cells have receptors for the Fc portion of immunoglobulin molecules or for complement components. Immunoglobulins bind to cells with Fc receptors which are avid for the Fc portion of the immunoglobulin molecules. The site is exposed after reaction with the specific antigen. C_3b is a product of cleavage of the third component of complement. It binds to specific receptors and mediates activation of other components of complement. One preliminary report indicates that these receptors are present (62). Other investigators could not demonstrate Fc or C_3b receptors on normal human pulmonary and umbilical vein endothelial cells in culture (63, 64). However, when these cells were infected with Herpes simplex virus (Type 1), they synthesized Fc and C_3 receptors (64).

Synthesis of Fc and C_3 receptors may be an adaptive function serving to enhance the clearance of foreign antigen associated with infection. However, it may be adaptative at a price, increasing the chance of vascular injury, especially if the quantity of circulating complexes are large. Immune complexes activate the complement cascade and certain components become associated with the complex. Chemotactic factors derived from complement components, especially C5a and C567 attract neutrophils to sites of complement activation. Those observations also imply that the vascular endothelium cannot be considered static with respect to its functions but can be influenced by as common an event as a viral infection. These findings may be especially pertinent to degenerative vascular disease since as is reviewed previously, virus infection have recently been shown to lead to atherosclerosis (45, 46).

Cellular and humoral immune reactions are believed to be important in the endothelial and arterial injury associated with graft rejection. The endothelium appears to be the primary target for injury in these instances probably because it has histocompatibility antigens on its luminal surface. Thus, cell mediated and/or humoral immune reactions could initially lead to damage to the endothelium with endothelial denudation. Subsequently, platelet reaction with the denuded luminal surface, smooth muscle cell proliferation and intimal thickening and lipid deposition would occur as outlined previously. In the instance of endothelial injury due to graft rejection, as in some instances and mechanical and chemical injury, this hypothetical sequence is supported by evidence obtained from experiments in which pharmacological agents were used to modify the immunologically-mediated graft rejection and the effect of platelets on the wall as noted above. Results of these experiments indicate that dipyridamole, an inhibitor of platelet aggregation, prevented graft-induced arteriosclerosis in kidney transplants and heart transplants in rats (65, 66).

The pathogenesis of the recently described model of virus-induced atherosclerosis is even less well understood. As noted above preliminary evidence suggests that focal accumulation of smooth muscle cells containing viral antigen are present in the media of the arterial wall as well as foci of necrosis sometimes surrounded by lymphocytes. These findings indicate that thickening of the arterial wall may at least in part be a consequence of the arterial necrosis and surrounding mononuclear reaction primarily lymphocytic. These findings also suggest that cell-mediated immune reactions may be important in the vessel injury. However, the possibility exists that smooth muscle cell proliferation and intimal thickening may be a direct result of the virus infection. Viruses, and particularly herpesviruses are known to enhance the proliferation of mesenchymal cells in tissue culture (67, 68). It is also possible that infection of smooth muscle cells with the virus may act as a mutagen and lead to neoplastic transformation and proliferation of cells as suggested by Benditt (69). In this regard it is important to remember that Marek's disease herpesvirus is an oncogenic virus and well known to cause lymphomas in chickens.

Having briefly considered the pathogenesis of the arterial injury and intimal thickening in these two models it is appropriate next to consider the question of lipid accumulation in the injured arterial wall. It is widely believed that arterial injury leads to lipid accumulation in the arterial wall as a result of disruption of the barrier function of the endothelium with increased filtration of lipoproteins.

Recently we have investigated the mechanism of lipid accumulation in the injured arterial wall. In these experiments we used the balloon-catheter model of injury to the rabbit aorta as described by Baumgartner. We specifically assessed and compared the quantity of lipid in the normal artery and in the de-endothelialized and re-endothelialized neointima of the injured aorta (Table I), (70, 71). Results of morphometric and chemical analyses of these arterial lesions indicated: 1) that arterial injury led to enhanced accumulation of lipid, in particular cholesterol and cholesteryl ester, and 2) that lipid accumulation was accentuated in the intima underlying regenerated endothelium and not in the de-endothelialized neointima as we had anticipated. Results of these experiments also indicated that in hypercholesterolemic rabbits the total cholesterol content of the aorta correlated with serum cholesterol concentrations in the re-endothelialized area of

TABLE I
Lipid Content of Injured and Uninjured Aortas

	CHOLESTEROL		CHOLESTERYL ESTERS	
	INJURED AORTAS			
	WHITE AREAS	BLUE AREAS	WHITE AREAS	BLUE AREAS
GROUP I (IN)	0.73 ± 0.20^{a}	0.65 ± 0.18	1.02 ± 0.30^{egh}	0.43 ± 0.11^{e}
GROUP II (IL)	3.04 ± 0.62^{abc}	1.32 ± 0.20^{b}	5.43 ± 1.20^{fgi}	2.25 ± 0.57^{f}
	UNINJURED AORTAS			
GROUP III (N)	0.47 ± 0.12^{d}		0.12 ± 0.05^{h}	
GROUP IV (L)	1.20 ± 0.19^{cd}		0.40 ± 0.09^{i}	

$\bar{X} \pm$ SE; ug lipid/mg wet tissue wt.

N = 9 for each experimental group

Values with the same letters are significantly different from each other (p 0.05)

IN, IL, N and L designate rabbit treatments including injury with lipid-poor diet, injury with lipid supplemented diet, untreated, and lipid-rich diet without injury respectively.

Modified from Falcone *et al.* (71), by permission of the American Journal of Pathology.

the injured aorta but not in the de-endothelialized areas over a range of serum cholesterol concentrations of approximately 900 mg/dl (Table II). Thus, results of these experiments indicate that arterial lipid accumulation following injury is not simply a result of increased filtration of lipoprotein across a de-endothelialized intimal surface.

We questioned whether this paradoxical lipid accumulation could result from 1) increased transport of lipid or lipoprotein by endothelium or alteration of lipoprotein, 2) alteration of the metabolism and the structure of the extracellular matrix with increased accumulation of extracellular lipid or 3) alteration of the metabolism of cellular components of the arterial wall with accumulation of intracellular lipid. We known of no evidence that endothelium enhances the transport of lipoprotein. In fact, results of several experiments including preliminary results from our own laboratory indicate that there is increased permeability to various substances in the de-endothelialized arterial wall (72−75).

TABLE II
Correlation of Aortic Cholesterol with Serum Cholesterol Concentration

	AORTIC SEGMENT	
	THORACIC	ABDOMINAL
BLUE	.05 n.s.	.22 n.s.
WHITE	.62 .01 P .025	.71 P .005

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In subsequent experiments, we tested whether or not there were alterations of the extracellular matrix that could lead to accentuated trapping of lipoprotein in the re-endothelialized neointima. We were able to demonstrate that over time there is increased accumulation of radiolabeled apo-B-lipoproteins in re-endothelialized areas of injured aortas as compared to adjacent de-endothelialized areas. Initially the concentration of radiolabeled lipoprotein was greater in the de-endothelialized areas but diminished in parallel with decreasing plasma concentration (75). We interpret these results to indicate the apo-B-lipoproteins are bound preferentially in the re-endothelialized areas and no longer in equilibrium with the plasma. Support for this interpretation comes from experiments in which we demonstrated by both morphometric and chemical analysis, that re-endothelialized neointima contains increased quantities of glycosaminoglycans (76, 77). This may explain the enhanced lipid accumulation since certain glycosaminoglycans have been shown to bind to low-density lipoproteins (78).

We have also recently investigated the effect of injury on cellular metabolism in the arterial wall (79). We assessed and compared the activities of several marker enzymes for cell organelles in homogenates from uninjured rabbit aorta as well as in re-endothelialized and de-endothelialized portions of injured aortas. Activities analyzed included a microsomal enzyme responsible for cholesteryl ester synthesis, acyl CoA:cholesterol

TABLE III

Cholesteryl Ester Metabolism in Injured and Uninjured Aortas

	ACID CHOLESTERYL ESTERASE ACTIVITY		ACYL CoA: CHOLESTEROL ACYLTRANSFERASE ACTIVITY	
	INJURED AORTAS			
	BLUE AREAS	WHITE AREAS	BLUE AREAS	WHITE AREAS
GROUP I (IN)	$13.5 \pm 1.6^{*\,ac}$	6.7 ± 1.1^{ade}	1.1 ± 0.2	1.1 ± 0.1^{h}
GROUP II (IL)	6.3 ± 1.2^{bc}	3.1 ± 0.5^{bd}	1.1 ± 0.1	1.0 ± 0.2
	UNINJURED AORTAS			
GROUP III (N)	0.5 ± 0.04^{ef}		0.3 ± 0.02^{gh}	
GROUP IV (L)	2.0 ± 0.2^{f}		0.7 ± 0.1^{g}	

* Specific Activity (mU Act./mg DNA) ± SEM.

Values with the same letters are significantly different from each other (p 0.05).

IN, IL, N and L designate rabbit treatments including injury with lipid-poor diet, injury with lipid supplemented diet, untreated, and lipid-rich diet without injury respectively.

Modified from Hajjar *et al.* (79), by Permission of the American Journal of Pathology

acyltransferase and a lysosomal enzyme responsible for cholesteryl ester degradation, acid cholesteryl ester hydrolase (79).

Results indicate that arterial injury leads to alteration in activities of cellular enzymes in the aortic wall, particularly enzymes responsible for synthesis and degradation of cholesteryl esters and that endothelium modulates these activities. Especially pertinent was a relative decrease in re-endothelialized areas as compared to de-endothelialized areas of the lysosomal enzyme responsible for cholesteryl ester degradation, acid cholesteryl ester hydrolase (Table III). Thus, the wall of re-endothelialized areas has a decreased ability to degrade cholesteryl ester even in the presence of increased accumulation of cholesteryl ester-rich lipoprotein. We believe that these findings may account for the increased lipid accumulation in the re-endothelialized areas.

Finally, stimulated by findings that neointimal smooth muscle cells in the de-endothelialized aorta synthesize increased quantities of prostacyclin, we investigated the effect of prostacyclin on lysosomal cholesteryl ester hydrolase activity and cholesterol content of cultured rabbit aortic smooth muscle cells. Results of these latter experiments indicate that prostacyclin and its stable end products, 6-keto PFG_1 and 6-keto PGE_1, stimulate activity of cholesteryl ester hydrolase activity and lead to a decrease in cholesterol content of cultured aortic smooth muscle cells (80). In summary results indicate that 1) arterial lipid accumulation following injury does not simply result from increased transport of lipoprotein across the de-endothelialized surface of an injured artery. 2) Arterial injury leads to alteration in the metabolism of the arterial wall and endothelium modifies these changes, and 3) Lipid accumulation in the injured aortic wall is a complex interaction between increased filtration of lipoprotein and metabolic perturbations within the wall.

In man, there is little evidence to suggest that endothelial injury occurs that is of sufficient magnitude to lead to large areas of endothelial desquamation. It seems more likely that injury induces small areas of endothelial desquamation. Experimental evidence from investigations of Reidy and Schwartz suggest that under the latter conditions the denuded surface rapidly re-endothelialized by migration of endothelial cells (81). One may then ask whether or not endothelial injury without denudation leads to alterations in arterial wall metabolism and lipid accumulation?

The answer to this very important question is unknown. However some experiments outlined above may furnish important clues. The extent of endothelial denudation observed in the serum-sickness model is probably not sufficient to account for the striking enhancement of lipid accumulation and it is likely that more subtle forms of endothelial injury may be important. Similarly, areas of intimal thickening resulting from previous episodes of immune-complex disease are at least in large part and probably completely, re-endothelialized. However, as discussed above these areas of intimal thickening preferentially accumulate lipid and evolve as atherosclerosis.

Finally, endothelial denudation does not appear to occur in our model of virus-induced atherosclerosis which is associated with arterial injury. However, lipid accumulation accurs in the injured aortas of these normocholesterolemic chickens.

Recent data suggests that this lipid accumulation in these virus-infected chickens may be a result of altered metabolism of smooth muscle cells in the arterial wall. These findings indicated that infection of cultured chicken vascular smooth muscle cells with Marek's disease herpesvirus enhances lipid accumulation in these cells, suggesting that infection with Marek's disease virus alters lipid metabolism. There was a 7-fold increase of cholesteryl ester in MDV-infected smooth muscle cells as compared to uninfected cells or cells infected with another avian herpesvirus, turkey herpesvirus (Table IV). There were also qualitative differences in the cholesteryl esters in the MDV-infected cells. Cholesteryl esters in MDV-infected cells contained primarily saturated fatty acids as compared to uninfected cells that contained primarily unsaturated fatty acids (82).

Epidemiological studies have established that diabetes mellitus in man is one of the risk factors associated with atherosclerosis (83, 84). Although occasional investigators have sought difference in arterial wall metabolism in diabetic arteries in an attempt to explain the increased risk in diabetes, most of the emphasis has been on changes in the patterns of circulating lipoproteins. Results of experiments summarized have indicated that immunologic and viral-induced arterial injury can lead to atherosclerosis and that alterations of arterial wall metabolism and in particular cholesteryl ester metabolism may contribute to the atherosclerosis seen following mechanical and virus-induced injury to the arterial wall. Diabetes mellitus is associated with changes in carbohydrate, protein and lipid metabolism and may be associated with arterial injury. It is possible that diabetes may lead to accentuated atherosclerosis because of altered arterial wall metabolism induced by arterial injury or that diabetes may alter the metabolic response of the injured arterial wall.

Support for this hypothesis comes from recent experiments of Wolinsky *et al.*, reported at this meeting. Results of these experiments indicate, that in the aortic wall of rats, streptozotocin or alloxan-induced diabetes leads to reduced activities of several enzymes including acid cholesteryl ester hydrolase (85). Insulin administered over a period of several weeks returned these metabolic changes to normal. Similar abnormalities of metabolism in arteries of human diabetics may lead to increased lipid accumulation, especially in the presence of increased serum lipoprotein. Alternatively, in addition, diabetes may alter the response of the arterial wall to other injurious stimuli and in this manner accentuate sterol accumulation. For example, Wolinsky and co-workers demonstrated that streptozotocin diabetes in rats will alter the metabolic response of the wall to hypertension induced injury (86).

TABLE IV

Cholesterol and Cholesteryl Ester Content of Cultured Aortic Smooth Muscle Cells

	CONTROL	INFECTED WITH HVT**	INFECTED WITH MDV**
CHOLESTEROL	1.00 ± 0.29*[a]	2.78 ± 0.23[a]	4.81 ± 0.87[a]
CHOLESTERYL ESTER	0.73 ± 0.15[b]	0.64 ± 0.10	4.94 ± 1.08[b]

* ug lipid/ug DNA ± SEM

** HVT and MDV represent Turkey herpesvirus and Marek's Disease herpesvirus respectively

Values with the same corresponding letters are significantly different (p 0.05)

Modified from Fabricant *et al.* (82), by permission of the American Journal of Pathology

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Intramural Pathology in the Diabetic Heart: Interstitial and Microvascular Alterations

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Primary myocardial disease occurring in the absence of extramural coronary artery atherosclerosis is now recognized as a significant complication of diabetes mellitus (1–13). Although probably outweighed by the effects of occlusive coronary disease on the diabetic heart, the existence of a specific cardiomyopathy causing congestive heart failure has been supported by a wealth of epidemiologic (8), clinical (7, 10–14), and experimental (6, 9) data. However, as yet, the pathogenesis of diabetic cardiomyopathy is unknown. Several investigators have proposed that this syndrome may be secondary to small vessel (intramural) coronary artery disease (6–9, 15–17); while others have suggested that accumulations of glycoprotein and collagen in the myocardium (9, 10), or metabolic alterations (6, 9) may account for the cardiac dysfunction. Despite these previous studies, diabetic cardiomyopathy has not been well characterized either clinically or pathologically. In particular, interaction between diabetes mellitus and other commonly associated conditions such as hypertension have not been investigated systematically for their potential causal role in the development of myocardial failure.

Within the past few years, we have had the opportunity to study a number of diabetic patients at postmortem who had a typical cardiomyopathic picture (18): large, failing hearts with minimal extramural coronary artery disease and striking interstitial alterations. These patients all had one clinical feature in common—the presence of long standing hypertension. Employing a semiquantitative analysis of the histologic changes in these hearts, the results suggested that hypertension is significantly related to the pathogenesis of severe diabetic heart disease. These data were supported by a concurrent study of an animal model which closely mimicked the clinical syndrome (19). This rat model also provided a means to investigate the relationship between the pathologic alterations of the myocardium, and possible dynamic abnormalities of the coronary microcirculation elucidated by special perfusion techniques (20).

Our studies of both the human and animal disease, which we have termed hypertensive-diabetic cardiomyopathy, have provoked numerous questions and, we believe, some fresh insight into the mechanisms of myocardial degeneration. Is there a cardiomyopathy directly related to diabetes mellitus, with observable histologic alterations of the myocardium? Is diabetic cardiomyopathy a diffuse myocardial disease, or is it limited to focal regions within the heart? If the latter is true, is the process mediated by so-called small intramyocardial vessels, or by the microcirculation which is not ideally visualized by routine histologic or ultrastructural techniques? If the microcirculation is involved, how can it mediate the variety of degenerative changes observed? Might similar processes be operative in other degenerative cardiac diseases, and might specific treatment be possible to abort or ameliorate these conditions? In the following discussion, data will be presented that begin to suggest answers to these questions.

The diabetic patients with severe congestive heart failure studied at autopsy (18), had several clinical and pathologic features in common. The patients were generally in their 6th or 7th decades, and were predominantly long-term (>10 years) adult-onset insulin-dependent diabetics.

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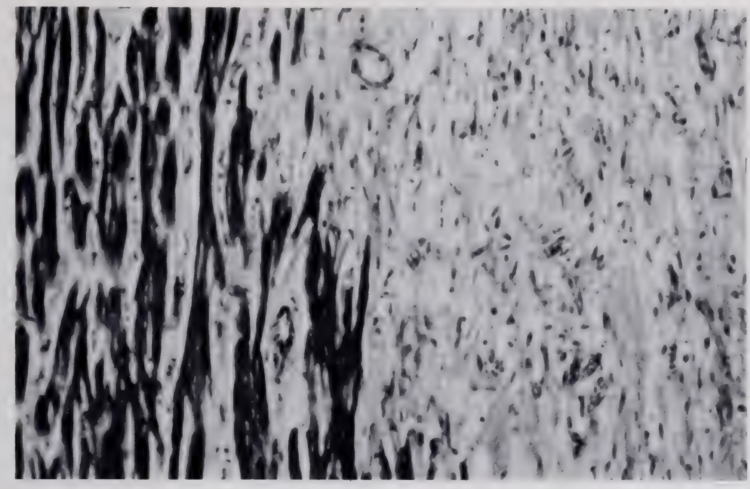

FIG. 1. A section of left ventricular myocardium, from a patient with hypertensive diabetic cardiomyopathy, reveals an area of organizing myocytolysis composed of vascularized collapsed stroma with early deposition of collagen. Multiple such areas were studied demonstrating that myocytolytic necrosis was the initial event in the development of focal replacement fibrosis, a characteristic feature of this disease. (Trichrome stain, original magnification ×32)

All but two had Kimmelstiel–Wilson renal disease. None had significant occlusive coronary atherosclerosis, yet atherosclerotic changes were common in other organs. Most important, all patients in this group were hypertensive.

Gross examination of their hearts revealed concentrically hypertrophied or dilated ventricles, with a firm consistency seemingly related to extensive myocardial fibrosis. No large scars consistent with previous myocardial infarctions were noted, despite the fact that several patients had this diagnosis made on previous hospitalization. Changes typical of myocytolytic necrosis in various stages of organization were apparent.

The histologic analysis revealed two cardinal features: extensive interstitial and replacement fibrosis focally present throughout the myocardium. The replacement fibrosis could be sequentially traced through various stages as having derived from myocytolytic necrosis. This latter process is typical of the effects associated with catecholamine administration and reperfusion injury of the myocardium. In contrast to coagulative necrosis, these foci are generally small, hemorrhagic, with a histiocytic response, and lead to cytoplasmic destruction with preservation of the interstitial stroma. Although myocardial fibrosis is usually described as a single process, interstitial fibrosis can be clearly differentiated from replacement fibrosis in that it is localized between *viable* myocardial cells and around small blood vessels. The different pattern of deposition suggests a different pathogenesis for these two forms of fibrosis.

In addition to these alterations, we observed two features concerning interstitial accumulations of PAS positive glycoprotein and small vessel abnormalities, which suggested that neither was significantly related to the clinical cardiac failure. For one, PAS positive material was not present diffusely in the myocardium as had been reported by Regan et al (9, 10), but was specifically localized to areas of scarring. For another, although small vessel changes were apparent in the hypertensive diabetics, comparison with control cases revealed no significant differences between the groups. Comparing the interstitial and replacement fibrosis, and the myocytolysis with hypertensive, diabetic, and normal controls, did, however, reveal significant differences. This suggested that hypertension had additive effects on the diabetic heart, and that the pathogenesis of myocardial degeneration in hypertensive diabetic cardiomyopathy could not be directly related to so-called small vessel disease.

To test the hypothesis that it is the combination of diabetes mellitus and hypertension which leads to marked myocardial degeneration, we studied a rat model of the human disease (19). Young rats were made diabetic with streptozotocin injection and hypertensive with single renal artery clip. These animals were studied after eight weeks of combined disease and were compared to diabetic, hypertensive, and normal control rats.

As with the human hypertensive diabetics, extensive interstitial and replacement type fibrosis were the predominant pathologic alterations noted in the combined disease. These changes were focal and heterogeneous. Not all animals were equally affected, although we could correlate the degenerative changes with the relative degree of cardiac hypertrophy. Myocardium in areas distant from the fibrosis appeared normal. This was confirmed at the ultrastructural level where the myocytes only had features consistent with active cellular hypertrophy. Consistent with our human observations, PAS positive glycoprotein was noted specifically associated with collagen deposition. This was apparent ultrastructurally as increased amounts of perisarcolemmal and pericapillary basal lamina proliferation in regions of scar.

Comparison with the control groups revealed striking differences, particularly between the hypertensive diabetic and the diabetic animals. The latter had no histologic abnormalities, either in the myocardium or intramural blood vessesl. Ultrastructurally, diabetic animals had only increased numbers of lipid vacuoles associated with mitochondria. In contrast, the hypertensive animals had qualitatively similar but quantitatively less severe and less frequent alterations when compared to the hypertensive diabetic group. Thus, the experimental study confirmed our clinical impressions, and supported the contention that hypertension has an adverse influence on the diabetic myocardium leading to extensive interstitial and spotty replacement scarring with associated glycoprotein deposition. The disease is focal, not affecting all myocardial cells, but rather causing small areas of cell necrosis with scar formation, and collagen deposition in the interstitium.

What mediates these localized changes? Their absence in severe diabetes mellitus without complicating hypertension argues against a direct metabolic influence. Could the degenerative alterations be related to "small vessel" disease? Analysis of the human hearts revealed no differences in the degree of vascular change in the vessels commonly identified in this category (50-1000 micron sized arteries) among the four

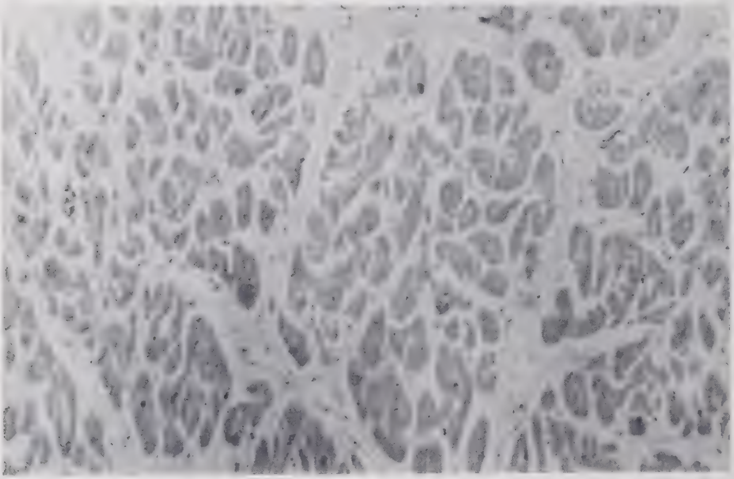

FIG. 2. Another section of left ventricular myocardium, from a patient with hypertensive diabetic cardiomyopathy, reveals diffuse, dense interstitial fibrosis surrounding viable, hypertrophied myocardial cells. In contrast to focal replacement fibrosis, secondary to myocytolytic necrosis, there was no evidence of cell necrosis in these zones suggesting a different pathogenetic mechanism for the development of this lesion. (Hematoxylin-Eosin, original magnification ×32)

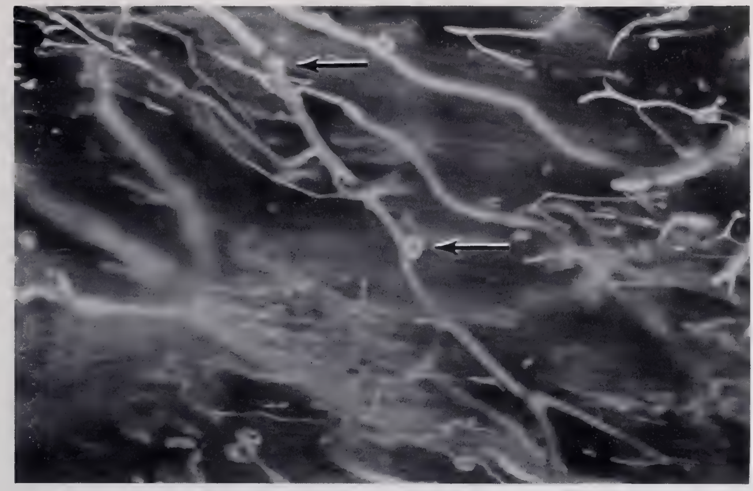

FIG. 3. A section from a silicone rubber perfused human diabetic heart reveals two microaneurysms (arrows) in an arteriolar sized vessel. The aneurysm in the center of the field has a grooved surface, similar to lesions described in retinal microaneurysms (22). (Epi-illuminated, cleared myocardium, original magnification ×32)

groups. Similarly, in the rat model, a comparison of vascular alterations demonstrated that the quantitative degree of change in the hypertensive animals with less severe myocardial degeneration, was significantly greater than the vasculopathy of the hypertensive diabetic animals with more severe myocardial lesions. Therefore, we concluded that small vessel disease could not account entirely for the experimental cardiomyopathy.

Concurrent with these studies, we were engaged in an evaluation of the human cardiac microcirculation employing silicone rubber (Microfil) injections at postmortem. To our surprise, in one patient, we identified microaneurysms in capillaries, arterioles, and venules identical to those described in diabetic retinal vessels (21). This patient had diabetes mellitus, and we embarked on a study of five other diabetics to confirm our observations. In three out of the six diabetic patients, we noted the presence of saccular and fusiform microaneurysms, which were not identified in any of eight age matched nondiabetic controls. These lesions could be clearly distinguished from artifactural changes. We were even able to recognize subtle structural variations that have been described in retinal lesions (22). What we could not do, however, was to correlate these abnormalities with specific regions of myocardial degeneration. Therefore, at best we could conclude that the capillary microaneurysm is a more generalized feature of the diabetic microcirculation that has been recognized previously, but we could not conclude with any certainty that it played a role in the development of diabetic heart disease.

Analysis of the human diabetic and nondiabetic microcirculations also revealed several other abnormalities, which at first we did not appreciate as significant. We noted tortuous or coiled vessels in both groups, as well as areas of pronounced microvascular narrowing. These latter lesions were much more common in the diabetic patients and were correlated with areas of interstitial and replacement fibrosis. They were often seen in relation to microaneurysms, in which the microaneurysms appeared to be a poststenotic dilatation of the vessel. Additionally, histologic study of the vessels in which these narrowings were observed, revealed that the vessels did not have an architectural distortion (that is, proliferation of endothelial or smooth muscle cells, or deposition of connective tissue) which could account for these focal lesions. Rather, we considered that these zones might represent regions of microvascular hyper-reactivity or a dynamic contraction of the

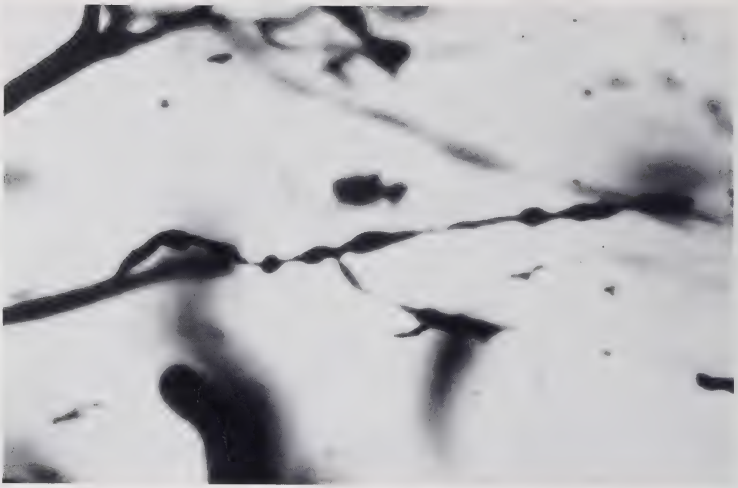

FIG. 4. A long arteriolar sized segment of silicone rubber perfused vessel, from a hypertensive diabetic rat, reveals numerous areas of beading resembling microaneurysms separated by pronounced zones of vascular constriction. Other studies of similar vessels demonstrated that these constricted regions were not due to pathologic alterations in the vessel wall, suggesting that the narrowing resulted from vascular hypercontraction. (Transilluminated, cleared myocardium, original magnification ×32)

vessel. Their relationship to areas of fibrosis suggested that they might have pathogenetic significance.

The next logical step was to perfuse our animal model with silicone rubber to carefully evaluate the microcirculatory changes in a controlled fashion. This study has recently been completed (20). We evaluated the same four animal groups studied previously: hypertensive-diabetic, hypertensive, diabetic, and normal controls. The silicone rubber filled microcirculation, particularly in the hypertensive diabetic and hypertensive groups, had a remarkable similarity to our human studies. Specifically, we observed saccular and fusiform microaneurysms in capillaries and pre- and postcapillary vessels. Beading of the microvasculature, coils, and single and multiple areas of constriction were observed. The constricted foci were often spatially related to microaneurysms. These changes were most prominent in the hypertensive diabetic and hypertensive animals, occasionally seen in diabetics, and only rarely in normals.

Because the techniques involved with visualizing the silicone rubber perfused vessels generally do not allow a concurrent evaluation of the tissue histology, we employed another method to approximate the three dimensional representation of the vasculature obtained with perfusion. Small portion of tissue were embedded in epoxy resin and were sectioned sequentially at 1 micron intervals. By following these serial sections over a 100 micron distance, changes in the surrounding tissue and in the vessel caliber and morphology could be ascertained.

This study, in a small number of animals from the four groups, revealed what we believe may be dynamic alterations in small vessels of severely affected animals. In particular, by following small arterioles, we occasionally noted a patent normal-sized lumen, followed a short distance away by partial or complete luminal closure without pathological changes in the vessel wall. These constrictions were often associated with interstitial fibrosis or edema in the immediate vicinity. Short distances away, the vessel re-opened and the interstitial alterations were no longer apparent. Thus, these serial studies mimicked the observation of focal constriction observed with Microfil perfusion. Myocytolytic necrosis may be a form of tissue injury due to reperfusion of blood supply mediated by vasoactive substances such as catecholamines (23). If the localized vascular constrictions represent markers of generalized mi-

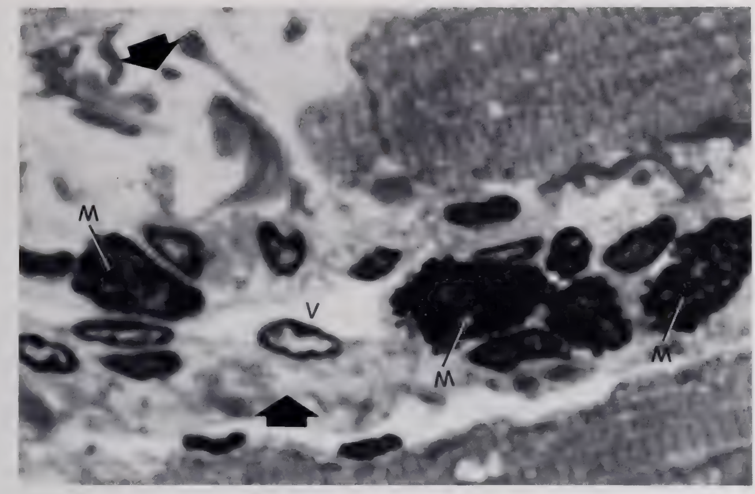

FIG. 5. An Epon embedded one micron thick section of myocardium, from a hypertensive diabetic rat, reveals a small vessel (V) surrounded by numerous dark, granule containing mast cells (M). The interstitium around the vessel has loose and dense connective tissue (arrows). (Alkaline toluidine blue, original magnification ×80)

crovascular hyperreactivity or spasm, it is possible that such dynamic events in these small vessels may lead to localized tissue damage followed by reperfusion when the vessel re-opens. Similarly, their constrictions, with their associated microaneurysms may increase the "leakiness" of the microvasculature, leading to localized interstitial edema, and stimulating collagen deposition in as yet unknown ways.

One other finding was appreciated when thin sections of tissue were examined serially: there were a large number of mast cells directly associated with the microvasculature. Mast cells are normal tissue components in the heart, and contain a variety of vasoactive materials including histamine. Quantifying these cells revealed approximately a two-fold increase in the hypertensive diabetic hearts when compared to the other three groups. Whether this increase in cells plays a role in vascular leakiness or the development of interstitial fibrosis remains speculative at this time.

These studies in both human and animal diabetic cardiac disease have suggested some answers to the questions posed at the beginning of this discussion. Our observations support the concept that it is the association of hypertension and diabetes that leads to significant pathologic degeneration and possible clinical symptomatology. Normotensive diabetes does not produce striking abnormalities in the heart. This has recently been confirmed by a biochemical study of collagen metabolism in streptozotocin diabetic rats in whom there was no increase in collagen synthesis in these animals (24). Our studies have also shown that hypertensive diabetic heart disease is a focal process manifested primarily by interstitial and replacement type collagen and glycoprotein deposition. This disease cannot be correlated with changes in what are normally called small intramyocardial vessels, but it is associated with several alterations in the microcirculation. These alterations include focal constrictions of vessels (hyperreactivity?, spasm?) which may mediate myocytolytic necrosis of small volumes of tissue. Increased reactivity, increased perivascular mast cells, and generalized leakiness of vessels in diabetes (25, 26) may lead to the deposition of interstitial connective tissue.

Finally, it is relevant to point out that we have observed similar microvascular abnormalities in the cardiomyopathic Syrian hamster, an animal model which gets reproducible lesions of myocytolytic necrosis with subsequent fibrosis (27). Both the degenerative myocardial lesions, and the microvascular hyper-reactivity can be prevented with a potent coronary vasodilator, verapamil (27). Similar treatment may be efficacious in hypertensive-diabetic heart disease.

Our investigations have, we believe, demonstrated that the combination of diabetes mellitus and hypertension produces significantly greater myocardial damage than either disease alone. That this is so should not be surprising, since there is now evidence that hypertension is associated with diabetic retinopathy (28) and diabetic renal disease (29, 30). Similarly, long term follow-up of diabetic patients spared severe complication, showed a low prevalence of hypertension (31). Thus our studies have added to this body of data, and have related the degenerative changes in the hypertensive and diabetic heart to microcirculatory alterations. If treatment of the experimental model is successful, it may provide a new mode of therapy for diabetic and hypertensive patients.

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Platelets, Prostaglandins, and Coagulation in Diabetes Mellitus

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Introduction

Recent theories have suggested that the process of atherosclerosis represents the response of the arterial wall to injury (1). At the site of vascular injury, there may be platelet adhesion, platelet aggregation with release of prostaglandins and their precursors, and thrombus formation. Diabetes is a disorder characterized by accelerated atherosclerosis. In view of this, it is appropriate to examine platelet function, platelet prostaglandin metabolism, and thrombus formation as they may be altered in the diabetic state. An increased understanding of these areas could help our perception of the process of atherosclerosis in diabetes mellitus.

Platelet Function in Normals

Platelet adhesion is a process whereby platelets stick to a site of vascular injury. One protein which is critical for this interaction between platelets and exposed subendothelial structures is von Willebrand Factor. This is a part of the Factor VIII complex and is found only in the endothelium, megakaryocytes, and platelets. In the absence of von Willebrand Factor, platelet adhesiveness is markedly impaired. A second factor of importance for platelet adherence to damaged vascular subendothelium is adenosine diphosphate which may be released by red blood cells and platelets following platelet aggregation.

Platelet plug formation occurs following platelet aggregation and secretion. Platelet aggregation can be induced *in vitro* by a variety of substances, many of which are probably also active *in vivo*. Those of probable physiologic importance are adenosine diphosphate (ADP), epinephrine, collagen, arachidonic acid, and thrombin. Platelet aggregation is also dependent upon calcium and may be induced by calcium ionophores.

After exposure to ADP, platelet aggregation occurs in two stages. At low concentrations of ADP, aggregation is confined to a short-lived phase which is reversible. At higher concentrations, platelets release intracellular materials and progress to irreversible aggregation. A similar sequence can be described for epinephrine and the first phase of aggregation induced by this agent is mediated by alpha adrenergic receptors. Collagen and thrombin activate platelet membrane phospholipases and thereby release arachidonic acid which is metabolized to prostaglandins and thromboxanes. The formation of these metabolites may mediate the aggregation response to low concentrations of these two agents but, with higher concentrations, the aggregation response is independent of arachidonic acid metabolism.

Platelets release a variety of intracellular materials which are stored in their granules upon stimulation by high concentrations of ADP, epinephrine, or by collagen and thrombin. Among these are ADP, serotonin, platelet factor 4, lysosomal enzymes, beta thromboglobulin, and a mitogen (platelet derived growth factor) which may stimulate cell proliferation. Released ADP probably acts to recruit other platelets to the site of injury and to promote further plug formation.

Platelet Metabolism of Arachidonic Acid

Prostaglandins and thromboxanes are 20 carbon fatty acids synthesized from essential fatty acids. Arachidonic acid (5, 8, 11, 14 eicosatetraenoic acid), an essential fatty acid is the precursor for the prostaglandins and the thromboxanes of the 2 series. In the platelet, as well as other tissues, prostaglandins and thromboxanes are not stored. Their precursors are stored primarily in membrane phospholipids. The rate limiting step

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in the synthesis of prostaglandins and thromboxanes is the release of arachidonic acid from its membrane storage sites, a step which is catalyzed by the enzyme phospholipase A_2. Phospholipase A_2 can be activated by a variety of stimuli, including aggregating agents such as collagen and thrombin and also simple mechanical trauma or membrane perturbation. Platelet phospholipase A_2 activity can be inhibited by dibutyryl cyclic AMP and the antimalarial drugs chloroquine, hydroxychloroquine and mepacrine (2–5).

Once arachidonic acid is liberated from its storage sites, it is metabolized by the fatty acid cyclooxygenase, formerly named prostaglandin synthetase, to form the labile cyclic endoperoxide intermediate, prostaglandin G_2. The fatty acid cyclooxygenase can be irreversibly inhibited by aspirin because it covalently acetylates the enzyme (6). Since the platelet cannot synthesize new cyclooxygenase, the inhibition of the activity of the enzyme lasts for the life span of the platelet. Platelet fatty acid cyclooxygenase is extremely sensitive to the inhibitory effects of aspirin. As little as 80 mg/day is enough to decrease platelet cyclooxygenase activity by 86%, and 325 mg/day (5 grains) produces over a 95% inhibition of activity (7). Therapeutic benefit as assessed by a decrease in thrombotic events occurring in arteriovenous shunts in hemodialysis patients has been achieved with as little as 160 mg/day (8). Indomethacin and other nonsteroidal antiinflammatory drugs reversibly inhibit the platelet fatty acid cyclooxygenase.

Prostaglandin G_2 is subsequently converted to prostaglandin H_2 which is converted to the various prostaglandins and thromboxane A_2. Both prostaglandin G_2 and H_2 are unstable with a half life of 4–5 minutes at 37°C in aqueous media. Prostaglandins D_2, E_2 and $F_{2\alpha}$ can be formed both enzymatically and non-enzymatically from the endoperoxides. The synthesis of prostaglandin D_2 and prostaglandin E_2 are quantitatively similar and prostaglandin $F_{2\alpha}$ is formed in smaller amounts.

Thromboxane A_2 is also formed from prostaglandin H_2 by the enzyme thromboxane synthetase and is synthesized in amounts ten to 100 fold greater than prostaglandin D_2 or E_2. Thromboxane A_2 is biologically active and extremely labile in aqueous media with a half life of ~37 seconds. It spontaneously rearranges to form the stable but inactive thromboxane B_2. In addition to thromboxane A_2, malonyldialdehyde and the 17 carbon fatty acid, HHT, are also products of the enzyme, thromboxane synthetase.

The other metabolic route of metabolism for arachidonic acid is via the lipoxygenase enzyme. The major products of this pathway in the platelet is HETE.

Prostacyclin (PGI_2) is another arachidonic acid derived metabolite which is synthesized by vascular endothelial cells but is not synthesized by the platelet (2). It is a potent antiaggregatory and vasodilator substance which has been hypothesized to be a physiological antagonist of thromboxane A_2 (2).

Role of Arachidonic Acid Metabolites in Platelet Function

The observation that washed platelets synthesized prostaglandin E_2 and prostaglandin $F_{2\alpha}$ when aggregated by thrombin stimulated considerable interest into the potential role of these substances in platelet function (9). Subsequently, it was shown that the aggregating agents, ADP, epinephrine and collagen stimulated platelet arachidonic acid metabolism to prostaglandins and thromboxanes (10).

The secondary or irreversible phase of platelet aggregation induced by low doses of ADP, epinephrine and collagen are dependent on the metabolism of arachidonic acid to a proaggregatory substance; since aspirin and other non-steroidal antiinflammatory drugs completely inhibit platelet aggregation and arachidonic acid metabolism by the fatty acid cyclooxygenase. Arachidonic acid added exogenously can cause platelet shape change, release and aggregation, all of which can be inhibited by aspirin or other nonsteroidal antiinflammatory drugs. However, prostaglandin E_2 and $F_{2\alpha}$ are not proaggregatory substances and prostaglandin D_2 actually inhibits platelet aggregation.

In 1974, Willis et al incubated arachidonic acid with sheep vesicular glands (a rich source of fatty acid cyclooxygenase) and demonstrated the presence of a labile substance(s) ($T_{1/2}$ = 5 minutes) which caused platelet aggregation when added exogenously to platelet-rich plasma (11). They named this material "labile aggregation-stimulating substance" and it was subsequently shown to be a mixture of the prostaglandin endoperoxides (G_2 and H_2). Subsequently, it was shown that the purified endoperoxides could stimulate aggregation and induce the release reaction. Hamberg and Samuelsson (12) and Smith et al (13) demonstrated that platelets formed the prostaglandin endoperoxides in response to thrombin. They also showed that the formation of the endoperoxides preceded the onset of aggregation thus establishing a potential role for these compounds in platelet aggregation. Hamberg et al (14) showed that if the endoperoxides were preincubated with human platelets, and the resulting incubate then rapidly transferred to another cuvette containing platelet-rich plasma, there appeared to be generated a more potent and labile proaggregatory substance. Subsequently, through a series of ingenious experiments it was shown that this substance was thromboxane A_2. Whether prostaglandin G_2 and/or H_2 must be converted to thromboxane A_2 to produce their aggregatory effects remains controversial (for a more extensive review see Halushka et al [5]). Finally, it appears that thromboxane A_2 and/or prostaglandin G_2 and H_2 can also cause platelet shape change.

Platelet Function in Diabetes Mellitus

Platelet Adhesion

Many older studies have shown increased platelet adhesiveness in the diabetic state (14). This has been shown with a variety of *in vitro* techniques, some of which also may measure platelet aggregation. Increased adhesiveness has been seen before established vascular disease, and has been reported in insulin deficient as well as noninsulin deficient diabetics.

Platelet Aggregation

There have been many studies of platelet aggregation in diabetes mellitus. One reason for this was the development of simple laboratory techniques for the assessment of this function *in vitro*. Generally, platelet-rich plasma is collected from an arm vein in patients and control subjects after an overnight fast. Critical concentrations of adenosine diphosphate, epinephrine, collagen, arachidonic acid, and/or thrombin are added to platelet-rich plasma. Aggregation is monitored by a change in optical density after adding the agent. Typical curves have been published (14, 15). A summary of most of the published studies in diabetics is given in several recent reviews (14, 16).

It is apparent from these studies that there is an increased sensitivity to platelet aggregating agents which can be shown in a number of diabetics. This finding is present in the majority of patients and studies when patients with established large or small vessel disease are studied. Some studies in animals (17–20) and man have suggested that these abnormalities may precede the development of vascular lesions. It will be important in future longitudinal studies to determine in man (14, 15) if these platelet defects precede or follow the vascular disease if one wants to understand their potential roles in the pathogenesis of atherosclerosis in diabetes.

Progress has been made in our understanding of some of the biochemical events which accompany the heightened platelet sensitivity in diabetes mellitus. Evidence has accumulated which implicates an altered platelet metabolism of arachidonic acid as playing a role in the enhanced aggregation. We found that aspirin (15) and eicosatetraynoic acid (21), another cyclooxygenase inhibitor, could significantly decrease the enhanced *in vitro* platelet aggregation associated with diabetes mellitus. Since intact platelet arachidonic acid metabolism is required for the second phase of platelet aggregation in response to some aggregating agents, the possibility existed that there was increased platelet metabolism of arachidonic acid in diabetes mellitus. We found that the platelets obtained from some diabetic subjects synthesized increased amounts of prostaglandin E like material in response to ADP, epinephrine, collagen and arachidonic acid (22, 23). Increased serum levels of prostaglandin E_2 and $F_{2\alpha}$ have been reported in diabetic subjects (26). Although the source of these prostaglandins is not known with certainty, presumably they are coming from the platelet. Subsequently, it was found that platelets obtained from pregnant diabetic mothers demonstrating enhanced platelet aggregation also synthesized increased quantities of malonyldialdehyde, an additional product of the enzyme thromboxane synthetase (25). Similar results have been found in a heterogeneous group of adult diabetics (26). In recent studies, an increased synthesis of thromboxane B_2 by platelets obtained from diabetic subjects has been found (27–29). It has also been found that thromboxane synthesis was positively correlated with the ambient plasma glucose obtained at the time of the study (27). The latter observation is consistent with a previous report of some reduction in enhanced *in vitro* platelet aggregation associated with strict metabolic control (30). There is no evidence to date to indicate a direct effect of glucose on *in vitro* platelet function per se, so the correlations with plasma glucose may simply be serving as an indicator of one or more additional metabolic abnormalities contributing to the altered platelet function. We have found that platelets obtained from diabetic subjects were less sensitive to the antiaggregatory effects of imidazole, a thromboxane synthetase inhibitor and 13 azaprostanoic acid, an antagonist of thromboxane A_2 and/or PGH_2 platelet receptor(s), suggesting the possibility that the increased platelet thromboxane synthesis may be contributing to the enhanced platelet aggregation (27).

The etiology of the enhanced platelet aggregation is certainly multifactorial. Since vascular disease is associated with enhanced platelet aggregation and platelet synthesis of prostaglandin endoperoxides (31) this has to be considered as one possible etiology. This may be particularly true in patients with thrombotic vascular disease and neuropathy. However, enhanced platelet aggregation has been reported in the absence of vascular disease.

A further piece of evidence against vascular disease being the sole etiologic factor came from the studies in rats and rabbits made diabetic by treatment with alloxan or streptozotocin. Within three days after becoming hyperglycemic, enhanced *in vivo* platelet aggregation was demonstrated (19). *In vivo* platelet survival is shortened and platelet thromboxane synthesis is increased in rats after streptozotocin treatment (17, 18).

In some diabetics, particularly those with advanced microvascular and macrovascular complications, the presence of factors which potentiate ADP-induced platelet aggregation of normal platelets have been found. Such activity was originally recognized in a diabetic patient who had multiple platelet thromboemboli and died because of disseminated intravascular coagulation and fibrinolysis (32). It has subsequently been recognized by several groups (32–38), while others report negative results (39–41). Partial characterization of several factors has been reported by two groups (37, 42). It has been suggested that one such factor in diabetes may be von Willebrand Factor (35, 37), while another may be activated by factor X (37). More work is needed in this interesting area of research.

One of the problems with assessing the importance of abnormal platelet behavior in the diabetic state is that most of the observations of abnormal platelet function have been made in the laboratory, using *in vitro* techniques on platelet-rich plasma. One must question the relationship of these findings to the actual *in vivo* situation in diabetic patients. Several lines of evidence suggest, however, that abnormal platelet behavior is operative *in vivo* in patients with diabetes mellitus. Early studies found that certain diabetics, particularly those with established vascular disease, had a larger percentage of large platelets (megathrombocytes) in the peripheral blood (23, 35, 43, 44). It is believed that increased numbers of megathrombocytes may indicate increased bone marrow production and release, secondary to an increased platelet turnover. Studies using labelled platelets have confirmed that increased platelet turnovers may occur in diabetics with established vascular disease (45, 46). Confirmation of these findings has been provided using the aspirin technique to assess platelet production (47). These findings indicate that some diabetic patients may be depositing platelets *in vivo,* leading to an increased production of platelets by the bone marrow.

Further evidence to support this point of view has been provided by measurements of plasma beta thromboglobulin (BTG), a platelet-specific protein, in patients with diabetes mellitus. Because BTG has a long half life, it can be used as an index of *in vivo* platelet aggregation and release. A number of studies have now shown elevated plasma levels of BTG in diabetes (48–51). Similar results have been reported for platelet factor 4 activity in diabetes mellitus (52). The exact relationship between this material and BTG is still to be determined, as is the relationship between platelet mitogens and BTG. Aside from the arachidonic acid metabolites (vide supra), other platelet release products have not been carefully studied in the diabetic state. In particular, in view of its postulated role in atherogenesis, studies of the platelet mitogen which stimulates smooth muscle cell proliferation (1) would be of great interest. A material released from platelets which is structurally similar to BTG and to platelet factor 4 has fibroblast growth-promoting activity (53); its effect on vascular smooth muscle cells have not been reported.

These findings are compatible with the idea that platelets may be aggregating *in vivo* and releasing intracellular materials into the circulation. The abnormalities of platelet function reported in diabetes are summarized in Table I.

Thrombosis in Diabetes Mellitus

The final stage in the artery diseased with atherosclerosis may be thrombus formation. While other papers should be consulted for reviews of this process in detail (54), it is appropriate to examine thrombosis as it may relate to the diabetic state. Thrombus size, measured *in vitro,* is greater in diabetics than in controls (55). Many of the coagulation factors have been found to be altered in patients with diabetes mellitus (56–59). Ele-

TABLE I

Platelet Function Abnormalities in Diabetes Mellitus

- Increased adhesiveness
- Hypersensitivity to aggregating agents
- Increased thromboxane production
- Increased production of PGE_2, $PGF_{2\alpha}$, malonyldialdehyde
- Platelet-plasma interactions
  - Platelet aggregation enhancing factor
  - von Willebrand Factor
- Increased platelet turnover
- Increased plasma beta thrombolgobulin levels

vated plasma levels of Factors V, VII, VIII, and X have been reported (56–59). The blood platelets may contribute to the coagulation sequence in several ways. Formation of even small amounts of fibrin will act to stabilize the platelet plug and stimulate further aggregation of platelets. Platelets may also activate Factor XI and thereby supply another source for thrombin generation and fibrin production. Increased plasma antithrombin III levels may be seen (59, 60), and can reflect counterregulation to excess thrombin or Factor X production. Increased plasma fibrinogen levels are regularly seen in diabetics, particularly those with microvascular complications (55–58, 61). Accelerated fibrinogen turnover has also been found (45, 57) and increased levels of fibrin split products may be seen (57). Fibrinolysis may be impaired (62–65).

In spite of these suggestive findings, it has not been possible to construct a cohesive scheme by which diabetes mellitus may contribute to a "hypercoagulable state." In fact, it is not possible to be certain that such a state exists, using *in vitro* techniques. On the other hand, in profound states of diabetic metabolic dysfunction, such as the hyperosmolar syndrome, it has been adequately demonstrated that disseminated intravascular thrombosis may occur (32).

Further, vessels plugged with fibrin have been seen in sural nerve biopsy specimens taken from patients with clinical evidence of diabetic neuropathy (66). We may conclude that virtually every segment of the coagulation scheme may be affected in diabetes, and further work may show that these collective abnormalities contribute directly to the accelerated vascular disease of diabetes mellitus.

The Problem in Perspective: Implications for Therapy

It must be recognized that these postulated events which may contribute to accelerated atherosclerosis in diabetes mellitus must occur in a dynamic fashion over a long period of time. Longitudinal studies in diabetics are generally lacking, so that a clear sequence of events can only be hypothesized from the available cross-sectional data. The heterogeneity of diabetes is such that group statistics which are generally reported in large series do not necessarily illustrate or predict behavior of individuals within the large group. Further, it is possible that such apparently important findings as abnormal platelet or coagulation behavior in diabetes may precede, follow, or even bear little or no relationship to accelerated vascular disease in diabetes mellitus.

There are a variety of approaches which might be expected to alter abnormal platelet behavior in diabetes mellitus. First, there is great interest in the possibility that alteration of the fat content of the diet may be a useful approach to modifying platelet function. Decreased platelet aggregability has been shown with starvation and with diets high in linoleate (67). Lengthened aggregation time and a shortened disaggregation time may occur within two to three days of starting a diet rich in linoleate.

It is possible that increased dietary cholesterol intake may increase platelet aggregability. Patients with marked hypercholesterolemia (type II hyperlipoproteinemia) show heightened platelet aggregation (68). Incubation of platelets with cholesterol-rich liposomes results in increased platelet sensitivity to aggregating agents and increased thromboxane synthesis (69). More studies are needed on the effects of modification of dietary fat, carbohydrate, protein, and calories on platelet function in diabetes mellitus.

Data on the effect of insulin on platelet function are conflicting. With acute administration of insulin, there are reports of enhanced (70) and diminished (71) platelet aggregability. Whether the changes are due to insulin itself, or some associated phenomenon such as changes in plasma catecholamines is not well understood. Insulin has no clear effect on platelet function in *in vitro* systems, suggesting it is not a direct effect of the hormone. One study has shown that correction of severe hyperglycemia with chronic administration of insulin to diabetics significantly reduced the enhanced platelet aggregation response to epinephrine (72). Platelet release, however, was not affected in this study and there were no corroborating studies or other prospective investigations using other aggregating agents. Cross-sectional data have shown no clear effect of insulin therapy on platelet function in diabetes.

Similarly, the data on sulfonylureas are not clear. Sulfonylureas will activate cyclase *in vitro* and can inhibit platelet aggregation *in vitro* (73) and *in vivo* (15). In alloxan diabetic rabbits, oral sulfonylurea therapy will lower platelet adhesiveness and aggregability (74). One study has suggested that oral sulfonylurea therapy will inhibit platelet aggregability in an outpatient setting (75). Other studies, usually of a cross-sectional nature, have shown no clear effect of sulfonylureas on platelet function. Clearly, more work is needed on the effects of insulin and sulfonylureas on platelet function.

In view of the exquisite sensitivity and long duration of effect of aspirin on platelet cyclooxygenase (vide supra), and the potential role of the platelet in vascular disease, interest has been generated to test the concept that aspirin may be beneficial in preventing the progression of diabetic vascular disease. This idea was given impetus by the demonstration of increased PGE_2 and thromboxane synthesis in platelets from diabetics. Several clinical trials to explore this idea are now underway. The first of these is a VA Cooperative Study on the effect of aspirin (325 mg tid) plus dipyridamole (75 mg tid) on the progression of lower extremity vascular disease in a group of adult male diabetics with recent amputations for gangrene. Dipyridamole may potentiate the antiplatelet action of aspirin in diabetes (19). The mechanism probably relates to its action to increased platelet cyclic AMP levels. There is evidence that this effect may require prostacyclin release by endothelium. The study began in 1976, and is a double blind placebo study with 186 patients in ten VA medical centers. Major end points are amputation for gangrene, death from vascular cause, and myocardial infarction. A second study, the Early Treatment for Diabetic Retinopathy Study (ETDRS), under the direction of the National Eye Institute is now underway. It will evaluate the efficacy of aspirin, 325 mg daily, to reduce the incidence and severity of background or preproliferative retinopathy in diabetic patients. In the context of this study, it is of interest to recall the observations of Powell and Field (76) who showed that the incidence and severity of retinopathy in a group of diabetic subjects with simultaneous rheumatoid arthritis on aspirin therapy was less than that seen in diabetic subjects without arthritis.

It is only through carefully designed prospective studies such as those described that we can determine if antiplatelet agents have any value in the prevention of large or small vessel disease in diabetes mellitus.

Approaches which utilize antithrombotic or fibrinolytic agents have not been systematically explored in diabetes mellitus. Experience with anticoagulant or fibrinolytic therapy for large vessel diseases in groups of patients some of whom were diabetic, have generally been equivocal or negative. Recent attention has focussed on earlier events in the process of atherosclerosis and thrombosis in hopes that therapy directed at these aspects of the problem may be effective.

It is apparent that we still have much to learn about atherosclerosis and its prevention in diabetes mellitus. However, with our increased understanding of the mechanisms involved in the production of vascular disease, it is encouraging to note that rational attempts to modify its course may be undertaken and may eventually prove to be successful.

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Is Insulin Atherogenic?

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The idea that insulin is involved in the development of atherosclerosis is based on two types of evidence: 1) epidemiologic and clinical evidence that atherosclerosis and conditions which increase the risk of atherosclerosis are associated with elevated insulin levels, and 2) experimental evidence that insulin affects the arterial wall which may be relevant to the development of atherosclerosis.

Epidemiologic and Clinical Evidence

The earliest reports of a relationship of insulin to atherosclerosis came from investigations of nondiabetic subjects with ischemic vascular disease. These studies showed that insulin responses to oral glucose tolerance tests were higher in subjects with ischemic heart disease than in subjects without this disease (1–2). Similar studies have been performed in a large variety of patients from different countries and they have consistently shown that subjects with ischemic heart disease (3–7), cerebral vascular disease (8), or peripheral vascular disease (9, 10) have elevated insulin responses to oral glucose. The insulin responses to intravenous glucose (7) or to intravenous tolbutamide (2, 4) have been less clearly elevated in the atherosclerotic subjects, suggesting that a gastrointestinal factor might be involved in the hyperinsulinemic response to oral glucose in subjects with ischemic vascular disease.

A number of questions arise from these studies. One is whether the abnormal insulin levels are a consequence of the ischemic damage to the tissues involved or whether they are associated with the arterial disease itself. This question has been answered by investigations of subjects with atherosclerosis but without complete occlusion of the artery and hence without tissue damage. These studies have shown that subjects with angiographically proven coronary artery disease (3), or peripheral vascular disease (9) without complete occlusion of the artery, have elevated insulin responses to oral glucose. It has been shown in other studies that in the acute phase of myocardial infarction and in congestive cardiac failure, depression of the insulin response to oral glucose is found (11), perhaps due to over-activity of the sympathetic nervous system.

Another question is whether the abnormal insulin levels precede the development of the arterial disease. This question has been answered in two ways. The insulin responses to oral glucose have been compared in populations with different incidences of vascular disease. In South Africa, the insulin responses to glucose in the white population were almost twice as high as those in the Bantu population, the white population having a much higher incidence of ischemic heart disease than the Bantu population (12). Edinburgh men have a higher incidence of ischemic heart disease than men in Stockholm. Although the glucose responses to oral glucose were identical in Edinburgh and Stockholm, the insulin responses to oral glucose were significantly higher in the Scottish men than in the Swedish men (13).

Three prospective studies have investigated the predictive effect of insulin in ischemic vascular disease. In Busselton, Western Australia, where a large community survey has been in progress for twelve years, it was found that for each glucose level there was a progressively higher risk of death from cardiovascular disease with rising insulin levels (14). The highest risk of cardiovascular death was found in subjects who had both elevated glucose and elevated insulin levels. In the Helsinki Policemen Study, the five-year incidence of the fatal and nonfatal ischemic heart disease was related to high fasting insulin levels, elevated insulin levels one and two hours after glucose, and increased total insulin responses to glucose (15). Multivariate analysis showed that the

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insulin response to glucose had the strongest predictive value for the development of ischemic heart disease. The Paris study showed that elevated insulin responses to glucose and high insulin: glucose ratios are predictive for ischaemic heart disease (16). There is thus clinical and epidemiologic evidence that elevated insulin levels are associated with atherosclerosis, that the abnormalities in insulin secretion are associated with the vascular disease itself, and that they precede the clinical appearance of the disease.

Diabetes is an important risk factor for atherosclerosis and the risk is independent of abnormalities in plasma lipids and blood pressure (17). The glucose intolerance which is the characteristic feature of diabetes is due to relative or absolute insulin deficiency. However, this does not necessarily mean that the tissues of the diabetic are exposed to low concentrations of insulin (18). Non-insulin dependent diabetics are frequently obese and obesity is associated with elevations of both fasting and postglucose insulin levels (19). When matched for weight, diabetics have lower insulin responses to oral glucose than nondiabetics. However, the majority of nondiabetics are thin, while the majority of noninsulin dependent diabetics are obese and hence diabetics will, on the average, be heavier than nondiabetics. Thus, many noninsulin dependent diabetics will have higher insulin levels than many nondiabetics. The majority of studies of atherosclerosis in diabetes have not taken into account the weight of the diabetics and the nondiabetic controls. However, two studies have shown that the large vessel complications of diabetes are associated with excessive weight gain or obesity (21). Mild diabetes of the type which is commonly associated with an increased incidence of atherosclerosis is often associated with high insulin levels (22). Thus, in assessing the various factors which may be involved in the increased incidence of atherosclerosis in diabetics, it is very important to take account of the severity of the diabetes, the presence or absence of obesity, and insulin levels.

The insulin-dependent diabetic with fasting hyperglycemia, a tendency to ketoacidosis, and absolute insulin deficiency, is treated with insulin. The dose of insulin administered to diabetics is considerably greater than the normal daily output of the pancreatic islets. There have only been a few studies of insulin levels in insulin treated diabetics and these, in general, have shown that insulin treated diabetics have higher insulin levels than nondiabetics (23, 24). Not only are the levels higher, but the regulation of insulin concentrations is abnormal. Thus, the normal healthy nondiabetic starts the day with a very low insulin level; this rises rapidly after the first meal but quickly drops again to low levels soon after the meal. Similar changes in insulin levels occur throughout the day and at night the levels again become very low. In contrast, the diabetic on insulin starts with a higher fasting insulin level. Following the insulin injection, the insulin concentration rises and remains elevated throughout the day irrespective of the meal pattern. Insulin levels take longer to fall to low values in the evening and remain elevated throughout the night (24). Thus, the insulin treated diabetic has higher insulin levels during many parts of the day than the nondiabetic. In addition, long-term treatment with insulin induces the formation of insulin antibodies. These antibodies will bind and probably inactivate some of the insulin resulting in an increase in the patient's exogenous insulin requirements (23). As a result, very high total insulin levels are found in the circulation of many insulin treated diabetics (23).

There have been very few studies of the relationship of the atherosclerotic complications of diabetes to insulin levels. One study in noninsulin dependent diabetics indicated that those with atherosclerosis had higher insulin responses to glucose than diabetics without vascular disease (7). Another study found little difference in the fasting insulin levels but, when insulin was expressed as a function of the simultaneously measured blood glucose level, the diabetics with atherosclerosis were found to have higher insulin to glucose ratios than those without vascular disease (21).

Experimental Evidence

A number of experiments using a variety of different techniques have shown that insulin has actions on the arterial wall which might be related to the development of atherosclerosis. Chickens fed a normal diet injected with insulin developed lipid containing lesions of the aorta (25). The vascular lesions were not associated with weight gain or changes in lipid levels. Insulin administration to chickens can also prevent the regression of experimental atherosclerosis which occurs when a cholesterol rich diet is removed, and can overcome the inhibitory effect of estrogens on experimental atherosclerosis (26). This type of experiment shows that administration of insulin promotes the development of lipid containing aortic lesions but does not indicate the mechanism by which insulin might influence the arterial lesion. Aortas removed from rats which had been rendered insulin deficient with streptozotocin incorporated less glucose into lipid than those removed from untreated animals (27). The insulin levels in the animals at the time the aortas were removed correlated with the uptake of glucose into the aortic lipids. In vivo injection of insulin into rats enhanced the incorporation of labelled glucose or acetate into aortic lipids (28, 29).

More recent experiments have used the cell culture system for both arterial smooth muscle cells and endothelial cells. The inner part of the artery, the media and the intima, are composed of only two cell types, the epithelial-like endothelial cells lining the lumen of the artery and the smooth muscle cells of the media. Both of these cells appear to have an important role in the pathogenesis of atherosclerosis (30). Endothelial cells normally act as a barrier preventing the entry of plasma constituents into the inner layers of the artery. If the barrier is breached then plasma constituents stimulate the proliferation of smooth muscle cells. Intra- and extracellular lipid, calcium and connective tissue are deposited as the fibrous plaque develops.

In cultured monkey aortic smooth muscle cells, the addition of insulin to the medium in successively greater concentrations resulted in a progressive stimulation of cell proliferation (31). The lowest concentrations of insulin used were similar to those found in the normal human circulation. To assess the effects of the native insulin in the serum it was passed through an affinity column coated with anti-insulin antibody. Compared with the same concentration of whole serum, cell proliferation was attenuated in the insulin-free serum medium, although the difference in insulin concentration was only 2–3 μu/ml. The proliferative effects of insulin were only found in cells early in culture life; in late culture life, no insulin effect was seen. Thus, the smooth muscle cell of the primate artery is sensitive to the proliferative effects of very small concentrations of insulin. Serum contains other potent growth factors as well as insulin as serum from which insulin had been removed still stimulates smooth muscle cell proliferation. Insulin also enhances incorporation of labelled acetate into sterols in cultured arterial smooth muscle cells (32). The absence of an effect when labelled mevalonate was the precursor suggests that insulin stimulates the activity of the enzyme HMG CoA reductase. Glucose had no effect on sterol synthesis in cultured cells, and glucagon only inhibited sterol synthesis when present in very high concentrations (33).

Insulin had no effect on incorporation of thymidine into DNA in cultured human endothelial cells (34). Endothelial cells also differ from smooth muscle cells in a number of other features, for example, in their requirement for homologous serum, and their response to the platelet derived growth factor. If the function of the endothelium is to act as a barrier, then it might be expected that its response to various stimuli would be different to that of smooth muscle cells and hence the difference in the response of the endothelial cell to insulin and to the platelet derived growth factor may be of pathologic significance.

Conclusion

A case can be made for insulin having a role in the development of atherosclerosis by both direct and indirect effects on the arterial wall. Elevated insulin levels related to obesity or to insulin therapy may act directly on the arterial wall causing smooth muscle cell proliferation and lipid deposition. Insulin may also act on the liver causing increased lipid synthesis and hyperlipoproteinaemia which may also cause lipid deposition and smooth muscle cell proliferation in the arterial wall (35). If these suggestions are correct, they indicate some approaches which may be effective in the prevention of atherosclerosis. Physical activity and avoidance of obesity will result in decreased basal and stimulated insulin levels, in both nondiabetic and diabetic individuals. The search for better and more physiologic methods of delivering insulin to diabetics who require this form of treatment should be encouraged.

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Role of the Autonomic Nervous System

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The autonomic nervous system plays a significant role in cardiovascular physiology and is essential in maintaining circulatory homeostasis. This function is mediated through vasomotor reflex mechanisms including the baroreceptors in the arch of the aorta and the carotid sinuses, its influence on secretion of blood and urinary catecholamines and sympathetically governed renin made available from the kidney. Since the autonomic nervous system is so often involved in diabetes, many of these reflexes are impaired or even abolished. As a consequence, there is an important effect of the circulatory system.

Since these two factors, namely autonomic nervous system neuropathy and arteriosclerosis are both so involved in determining circulatory response and because they are both so frequently and simultaneously present in the diabetic, the possibility of their interacting or influencing one another looms as a distinct possibility. Many new developments suggest such an interplay may indeed exist.

The possible relationship to arteriosclerosis is emphasized because arteriosclerosis in diabetes is characterized by increased frequency, earlier onset, accelerated progression, more extensive involvement, a lack of correlation with the severity or the control of the carbohydrate metabolic abnormality and obliteration of the sex difference in that the diabetic female is at equal risk with the diabetic male in this regard. The remarkable disparity in frequency of these complications in the diabetic versus the nondiabetic is yet to be satisfactorily explained including the absence of any demonstrable histopathologic differences in the arteriosclerosis of the diabetic and nondiabetic patients.

There is an increasing awareness of the occurrence of autonomic nervous system neuropathy in the diabetic associated with deleterious affects on physiologic functions. A great impetus in this regard has resulted from the recent development of a new generation of tests that are simple, noninvasive and reproducible. Prior to this, assessments of autonomic nervous function were usually complex, difficult to interpret and lacking in control of measurements. The newer methods may be classified into 1) tests based on the heart rate, including the Valsalva maneuver, beat-to-beat variation during deep breathing, standing or lying, heart rate response to standing, heart rate response during apneic facial immersion; 2) tests based on blood pressure including a response to muscle exercise and standing; and 3) response to drugs including phenylephrine or nitroglycerin that measure baroreceptor function and atropine and propanolol producing cardiac blockade. Some drugs can chemically dissect the input of the parasympathetic versus the sympathetic components of the autonomic nervous system.

Macroangiopathy can be anatomically divided into three broad aspects, namely the cerebrovascular, myocardial and peripheral.

Cerebrovascular Aspects

The blood supply to the brain is very carefully maintained. When blood pressure falls, several mechanisms come into play insuring adequate cerebral blood flow. Reflex venous and arteriolar constriction are necessary for the normal maintenance of the cardiac output and arterial pressure in the upright position (1). In health, blood and urinary catecholamines, adrenalin and noradrenalin, increase for the change from the horizontal to the vertical position (2). In addition, sympathetically mediated renin becomes available from the kidney (3). These reactions are mediated through the baroreceptors which are stimulated by a fall in bloood pressure with upright posture. This triggers signals via the vasomotor center of the brain to the autonomic nervous system resulting in increased cardiac output and vasoconstriction, thus returning blood pressure toward nor-

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mal. With a more severe decrease in the blood pressure, as occurs during shock, chemoreceptors in the carotid and aortic bodies respond to hypoxia and hypercapnea with vasomotor constriction via the autonomic nervous system, resulting in an increase in blood pressure.

Autonomic neuropathy in diabetes may significantly interfere with these mechanisms. Specifically, involvement of sensory baroreceptors (4), reduction of catecholamines (5), the inability of massage of the carotid sinus to evoke change in pulse rate or blood pressure (6), abnormal handgrip response (7), lowering of plasma renin (3), failure of plasma renin to increase (3), and the absence of compensatory tachycardia (8) have all been well documented. Failure of these mechanisms singly or, more commonly, in combination may lead to orthostatic hypotension. Whereas under most circumstances of significant fall in blood pressure there is some degree of compensatory tachycardia, patients with true orthostatic hypotension do not exhibit such tachycardia, and this is one of the major factors leading to vertigo and syncope secondary to a decrease in blood flow (9). The absence of reflex venous and arteriolar constriction is responsible for the marked impairment of postural adjustment leading to syncope. There is evidence that pressor catecholamine insufficiency is correlated with postural hypotension in familial dysautonomia (5). In patients with postural hypotension there is little or no increase in blood and urinary concentrations of catecholamines, a clear indicator of failure in the chain of events leading to necessary vasoconstriction. Contrary to what happens to the healthy person, change from the horizontal to the vertical position is not accompanied by an increase in blood and urinary catecholamines. It has been demonstrated that diabetic individuals with orthostatic hypotension have a significantly low plasma renin-like activity (3).

It is of special interest that a patient with amyloidosis and orthostatic hypotension was found to be depleted of catecholamines in the peripheral adrenergic nerve endings (10). Thus, orthostatic hypotension in amyloidosis may similarly result from diffuse autonomic neuropathy independent of amyloid infiltration, objectively demonstrated to be related to catecholamine depletion and directly comparable to diabetic autonomic neuropathy.

In summary, involvement of the normal regulatory homeostatic mechanisms by autonomic neuropathy is the basis for orthostatic hypotension leading to diminution of cerebral blood flow, resulting in cerebral anemia and syncope. In more severe instances, and superimposed on cerebral arteriosclerosis, it probably leads to transient ischemic attacks or cerebral infarction.

Myocardial Aspects

The principle differences between coronary arteriosclerosis in the diabetic as compared with the nondiabetic patient are an increased incidence in both dead and living patients; a striking increase in coronary heart disease in the diabetic female, including those who are normotensive, premenopausal, and free of significant hyperlipidemia; a higher early mortality rate; a shortened life among diabetic survivors of acute myocardial infarction; and a higher incidence of painless acute myocardial infarction in the diabetic individual (11).

The effects of autonomic nervous system neuropathy on cardiac function in the diabetic patient are numerous and well documented. These are measured by relatively simple methods that are noninvasive, nonpainful, and may frequently be done at the bedside. They include the demonstration of abnormal Valsalva maneuver (9, 12, 13), absence of compensatory tachycardia (8), resting tachycardia (14, 15), loss of beat-to-beat heart rate variation (15–18), the lack of response of the pulse rate or blood pressure to massage of the carotid sinuses (6), a failure of the heart beat to accelerate after intravenous atropine (15), abnormal handgrip response (13), arrhythmia (19), cardiac arrest (19), and histopathologic evidence of autonomic cardiac nerve involvement both on light and electronmicroscopy (20).

Sharpey-Schafer and Taylor (9) found that 20 percent of their patients had impaired circulatory reflex responses on the basis of the Valsalva test. Ewing et al (13) found that both the Valsalva and handgrip tests were useful in providing objective assessment of the integrity of the autonomic nervous system in diabetes mellitus. Other authors have made similar observations (12, 15). Resting tachycardia has been amply documented. In one report, three out of six cases had a heart rate of 100 to 110 beats per minute (21). The loss of beat-to-beat variation of heart rate during both quiet and deep breathing have been demonstrated by several authors. Most studies agree that the R-R interval variation is a better indicator of autonomic nerve damage than the R-R interval.

Resting tachycardia, the failure of the heart to accelerate normally after intravenous atropine, the absence of reflex bradycardia as well as the absence of sinus arrhythmia and the decreased variation of the R-R interval all clearly point to involvement of the vagus nerve (15). As a consequence there is the added tendency to cardiac dysrhythmia including spontaneous cardiac arrest. One patient with a totally denervated heart had tachycardia, a fixed heart rate, and a tendency to cardiac dysrhythmia (22). In one study, spontaneous cardiac arrest in three patients with severe autonomic neuropathy was observed (22).

A documented common clinical observation indicates that there is an increased occurrence of either painless acute myocardial infarction in the diabetic patient or a significant diminution of pain. In one study of patients with painless myocardial infarction, diabetes was the most frequent cause (23). This clearly suggests involvement of the autonomic nervous system as the afferent part of the reflex arc. This has been further established by the demonstration pathologically of the presence of autonomic nerve involvement at autopsy in diabetic patients with painless myocardial infarction (20).

Blunting of pain in the ischemic heart in the diabetic with arteriosclerosis leads to these patients with myocardial infarction being frequently admitted directly to the ward, bypassing the coronary unit. Thus, it may delay diagnosis and help contribute to the poor prognosis.

Cardiovascular responses to physical exercise are impaired in diabetic autonomic neuropathy. Resting heart rate is higher and the increase in heart rate for a low work load is diminished in patients with autonomic neuropathy compared to control patients. Maximum heart rate, maximal systolic blood pressure, maximal oxygen uptake and the greatest tolerable work load were reduced in patients with neuropathy. This would suggest the need for a greater stress for the heart and the cardiovascular system in general in performance of comparable work load.

The tissue concentration of noradrenlin which reflects sympathetic innervation is found to be considerably reduced in specimens of both hearts and arteries obtained from long term diabetics at postmortem (24). The depletion of the noradrenlin stores in the heart indicates that an important supportive mechanism is lost in the long term diabetic patient with autonomic neuropathy. This is probably of importance in stress especially after acute myocardial infarction when a highly active sympathetic nervous system is necessary for the maintenance of an adequate myocardial performance and the cardiac dennervation may contribute to the high mortality observed in the diabetic patient.

The presence of resting tachycardia suggests increased demand on the heart resulting from the extra persistent pumping effort that is required. All the other autonomic neuropathic effects help increase the loss of ability to alter the rate and amount of blood flow from the heart in response to physiologic and nutritional demand of tissue. The possibility that this imbalance may contribute to the increased morbidity and mortality rates of myocardial involvement in the diabetic is an attractive and logical possibility.

Diabetic Foot

The diabetic foot is characterized by wet gangrene, which can occur only in the presence of available circulating blood, as distinguished from the mummified gangrene of the nondiabetic individual that results from virtually complete absence of blood supply. In addition, some ten percent of amputations in diabetics are performed in the presence of palpable pulses. These facts denote that amputations may be indicated in the diabetic patient even in the presence of measurable circulation. On further analysis, it is evident that the chief single difference between the diabetic and nondiabetic foot is the presence of neuropathy in the former and its absence in the latter. It is well recognized that the sensory impairment of diabetic neuropathy permits unperceived minor trauma to occur which can lead to secondary infection, gangrene, and amputation (25, 26). This is enhanced by fluid loss or perspiration, dryness, and cracking of the skin. In addition, there are important abnormalities of vasomotor function which have not been heretofore adequately appreciated in the development of this complication. Martin demonstrated the loss of vasomotor response in diabetics with neuropathy (27). There was no increase in blood flow after heating in the patients with diabetic peripheral neuropathy. However, an injection of tolazoline (priscoline) acting directly on the smooth muscle of the vessel resulted in a sharp increase in blood flow, indicating that the defect was neuropathic and not a result of occlusive vascular disease. Moorhouse, Carter, and Doupe investigated physiologic aspects of vasomotor function and demonstrated abnormal vascular responses in diabetic peripheral neuropathy as well as the fact that denervated blood vessels displayed hypersensitivity to cold (28). Reflex vasomotor responses in the feet were completely absent in diabetic subjects with peripheral neuropathy. Rundles (29) emphasized autonomic disturbances in diabetic neuropathy, stressing changes in the skin temperature and sweating as detected by the starch-iodine test as well as reversal in the gradient of the skin temperature. Christensen measured resting blood flow patterns that indicated the presence of varying, undulating, beat-to-beat change of arterial flow (30). However, in diabetic patients with peripheral neuropathy there was complete loss of spontaneous variation, indicating that in the presence of peripheral autonomic neuropathy the ability to make necessary physiologic accommodations, to maintain homeostasis, and to meet local demand of tissues that vary from moment to moment has been severely impaired or lost.

Respiratory Aspects

Cardiorespiratory aspects have been observed in relatively young patients with severe autonomic neuropathy, with subsequent death in some of them. The patients become apneic and pulseless but will respond rapidly to resuscitation. In many episodes there was interference with respiration by drugs, anesthesia, or pulmonary infection suggesting that the arrests were initiated by the affected respiratory rather than cardiovascular reflexes. This may account for some of the sudden and unexplained deaths in diabetic autonomic neuropathy (31).

Comment

Abnormalities relating to autonomic nervous system disturbances in diabetes were described many years ago. These include sweating disturbances, abnormal temperature changes associated with postural hypotension, and vasomotor and trophic signs (32–34). More recently Rundles elaborated this concept and described many of the clinical symptoms (29). The intimate relationships between autonomic nervous system involvement and the syndromes of diabetic anhidrosis (35), diabetic gastropathy (36), diabetic diarrhea (37), diabetic neurogenic bladder (38), retrograde ejaculation (39), and impotence (40) have been delineated.

The important advances in understanding autonomic nervous system involvement has led to an appreciation of its role in the regulatory phenomena of the cardiovascular system. The development of sophisticated tests that are not only noninvasive, nonpainful and simple in performance have been remarkably informative and highly instrumental in establishing a significant body of information.

Anatomic evidence of autonomic nerve involvement in diabetes is supplied by the interesting observations of Grover-Johnson, Pearson and Kim (41, 42). Employing ultrastructural quantitation of the terminal innervations of small caliber blood vessels in patients with longstanding diabetes, they observed that the nerve endings are either entirely absent or are found at a significantly greater distance from the affected sites. They infer that the findings account for some of the vasomotor disturbances seen in diabetic patients. Anatomic evidence of a lack of end organ innervation in the peripheral blood vessels may be an indication that autosympathectomy occurs in diabetes mellitus.

Thus arteriosclerosis is not the only link between diabetes and its cardiovascular complications. Neurogenic factors may adversely affect cardiovascular hemodynamics in the diabetic patients. Altered responses to physiologic, psychologic and pharmacologic stimuli may present serious clinical problems.

The facts cited in this report indicate impairment of the diabetic individual with autonomic neuropathy to respond in normal physiologic fashion to the demands placed on the cardiovascular system. He has lost the capacity to adjust blood flow to respond to local tissue needs and hence this protective feature is eliminated. This interference with regulatory power limits the ability to maintain homeostasis. It is reasonable to suspect that with the development of vascular disease otherwise relatively asymptomatic autonomic neuropathic defects may play a role in producing transient ischemia or even infarction. Thus it may accelerate, precipitate or act as a modifying determinant of vascular pathologic conditions. In the brain, this could lead to cerebral ischemia and cerebral infarction; in the heart, arrhythmias and conduction defects could lead to cardiac arrest or myocardial infarction; and in the foot gangrene may result.

There is indirect evidence to suggest that this does take place. In a prospective study it was demonstrated that the death rate of diabetic persons with severe autonomic neuropathy was two and one-half times that of those diabetic individuals without comparable autonomic neuropathy (43). Thus simple autonomic function tests may serve as a reliable guide to prognosis. Czyzyk and Krolewski in a study of hospitalized patients with myocardial infarction documented a twofold increased mortality in the diabetic versus the nondiabetic patient (44). They were unable to correlate this marked increase with either shock, pulmonary edema, etc., but were able to make a definite correlation with the presence of arrhythmia and/or conduction defect. Arrhythmia and even cardiac arrest in diabetic patients with advanced autonomic nervous system involvement has been observed (45).

A new dimension has been added by observations indicating differences in the nature of autonomic nerve involvement. Specifically, it has been shown that the sympathetic and parasympathetic components need not be equally affected in the early phases of autonomic neuropathy. Thus an opportunity to determine rates and types of progress of these two parts of the autonomic nervous system is now available and hopefully will shed light on these problems (46−43).

Conclusion

Autonomic nervous system neuropathy has deleterious effects on physiologic functions of the blood vessels and circulation. This in turn may lead to impairment of normal homeostasis mechanisms and interfere with responses necessitated by the continually fluctuating demands of local and distal tissues. These abnormalities superimposed on a pathologic vascular system could play a definitive role in the marked increase in vascular related pathologic conditions in the diabetic patient which is now the leading cause of morbidity and mortality in diabetes. Since male and female diabetic individuals are at equal risk for the development of diabetic neuropathy, this could be a clue to understanding the elimination of the sex difference in the frequency of these complications in the diabetic patient.

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Diabetes and the Heart

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Diabetes mellitus is one of the leading public health problems in the industrialized world, and has a profound effect on the cardiovascular system. The morbidity derived from diabetes is largely related to its cardiac and vascular complications. We shall discuss the risk of heart disease among diabetics, the types of heart disease occurring in diabetes, and the therapy of heart disease in diabetic patients.

Risk of Heart Disease of Diabetes Mellitus

Coronary Atherosclerosis

The clinical manifestations of coronary atherosclerosis appear to be more common among diabetics than among control groups, the prevalence at autopsy being at least two fold in diabetics (1, 2). The Framingham Study (3) showed a distinct excess development of every clinical manifestation of coronary heart disease in those with impaired glucose tolerance, the risk of myocardial infarction being particularly increased. The incidence of occlusive peripheral vascular disease and congestive heart failure was higher than the incidence of coronary heart disease. Some have suggested that the increased risk of coronary disease among diabetics is related to the lipid abnormalities and the hypertension that accompanies diabetes mellitus (4, 5), but the Framingham study suggests that the incidence is increased beyond the risk imposed by these two conditions (3). The same was found in the Coronary Drug Project (6).

The incidence of coronary disease correlates more with the duration of diabetes than with its severity, but this relation may be equivocal since the duration of symptoms often has a poor correlation with the duration of the chemical abnormality.

Diabetes accelerates the appearance of atherosclerotic lesions by 10–12 years, and does so even more in women. In diabetes, coronary disease is as common in women as it is in men. The increased incidence in women includes those who are premenopausal, normotensive and with normal lipids (7). Among persons with premature atherosclerosis of the coronary arteries there is a large number with preclinical diabetes (8).

Although silent myocardial infarctions have often been noted among diabetics, the higher incidence does not reach statistical significance (9). Congestive heart failure after myocardial failure is more common in diabetics than in non diabetics (2); mortality during acute myocardial infarction is higher and long-term survival is poorer (10).

The incidence of congestive heart failure in the Framingham study (3) according to diabetic status revealed a two to four-fold increased risk in men and a five-fold increased risk in women. The increased risk is not explained by coexisting clinical coronary diseae, hypertension or hyperlipidemia. Although still a controversial issue, the Framingham data suggest that the increased risk of congestive heart failure is limited to the insulin treated patients (3). Others have also reported an increased incidence of congestive heart failure in diabetes (11, 12).

Types of Heart Disease in Diabetes

Cardiac pathology often found in diabetics includes coronary atherosclerosis, vascular disease, and cardiomyopathy. Patients with diabetes have been reported to have a higher incidence than nondiabetics of bacterial endocarditis, myocardial abscesses in cases of sepsis, pericarditis in those with renal failure, and hypokalemic myocarditis in those with acidosis.

Atherosclerosis of the Coronary Arteries

The atherosclerotic lesions in the diabetic patient are identical in nature to those seen in the nondiabetic, with a similar preference to be localized in the proximal segments of the coronary

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arteries. The only difference is that atherosclerosis appears earlier in life in the diabetic than in the nondiabetic (13), so that for age matched populations, diabetics have more severe and more diffuse atherosclerosis. The angiographic appearance of coronary atherosclerosis is also identical to the one in nondiabetics. A possible difference exists in that it has been suggested (14) that diabetics have less collaterals than nondiabetics for the same degree of atherosclerosis.

There is experimental evidence that insulin stimulates proliferation of the smooth muscle cells of the vascular wall, setting the stage for the development of the atherosclerotic plaque. Although the endothelial cell is resistant to the effect of insulin, its permeability changes with a number of factors (for example, increased catecholamines during fluctuation of blood glucose levels), permitting the smooth muscle cells to get exposed to insulin. In addition, insulin inhibits lipolysis and promotes synthesis of cholesterol, phospholipids and triglycerides in the vascular wall.

Diabetic Vascular Disease in the Heart

Two lesions are seen in the diabetic heart, endothelial proliferation of the small vessels and a microangiopathy affecting the capillaries.

The term "small vessel" applies to those coronary vessels with a diameter of 20 to 500 microns. Histopathologic studies have shown that diabetics have narrowing of the intramural coronary arteries (14–16), produced by a characteristic endothelial proliferation which could explain some of the ischemic manifestations of diabetes in the heart and the extremities (17). The problem in attributing common ischemic manifestations to small vessel disease is the difficulty in quantifying the extent and the physiologic significance of the process.

The changes seen in small vessels of diabetics include (18, 19): a) endothelial proliferation producing lumps, bridges, mounds, and papillary projections, b) subendothelial fibrosis and proliferation of the elastica, and c) hyalin deposits in the media. These changes have been seen in 72% of diabetic hearts, but also found in 36% of nondiabetic hearts (19). Others (20) have found similar lesions in 40% of random, unselected autopsies. Moreover, in amyloidosis (21), endomyocardial fibrosis (22), and immune arteritis small vessel disease has been described without an association to myocardial fibrosis. That small vessel disease in diabetes may not have direct relationship to myocardial pathology is supported by a recent publication showing no small vessel disease in the free wall of the left ventricle of diabetics (23).

Microangiopathy

A thickening of the basement membrane is found in the capillaries of the myocardium as well as the capillaries of the glomeruli, the retina, the brain, the pancreas and the conjunctiva (23–24). It is possible that this microangiopathy contributes further to the abnormal myocardial perfusion of the diabetic heart.

Diabetic Cardiomyopathy

Among patients with idiopathic cardiomyopathy, there is a significant increase in the frequency of diabetics (18). Although congestive heart failure in the diabetic is most often caused by atherosclerotic or hypertensive heart disease, a specific form of cardiomyopathy affects the diabetic heart (25). These patients often have small vessel disease with normal large coronary arteries, and they show extravascular deposition of collagen, triglycerides and cholesterol with normal muscle cells, all suggestive of a nonischemic cardiomyopathy.

Regan (26) studied 13 subjects with diabetes at autopsy. He confirmed the above findings, and noted a positive periodic acid-Schiff staining material in the interstitium, collagen accumulation in perivascular spaces and between the myofibers, increased cholesterol and triglyceride deposits, and normal epicardial coronary arteries. These increased deposits of lipids in the myocardium occured in spite of normal lipid plasma levels (27).

Diabetic cardiomyopathy is associated with abnormalities of left ventricular compliance and function. They are reflected in shortening of the left ventricular ejection time, prolongation of the pre-ejection period and elevation of the ratio PEP/LVET (28). Left ventricular diastolic pressure is elevated without elevation of diastolic volumes.

This cardiomyopathic process in the diabetic heart may explain in part the higher mortality and the frequent occurrence of failure during acute myocardial infarction.

Infants of diabetic mothers have cardiomegaly or heart failure in about fifty percent of cases (29). This form of cardiomyopathy seems to be transient.

Diabetics with coronary disease often present with more left ventricular dysfunction than expected from the specific coronary artery obstructions. This finding is also consistent with the presence of an underlying cardiomyopathic process.

Diabetic neuropathy

Diabetic neuropathy involving the cardiovascular system is frequent among patients with peripheral neuropathy, but is often asymptomatic (30–32). It is specially common in patients with signs of autonomic dysfunction such as diarrhea, impotence, delayed gastric emptying or anhidrosis.

There is a fixed resting tachycardia that fails to respond to physiologic maneuvers, like Valsalva, carotid sinus pressure, handgrip, tilting and others. There is also a loss of the normal sinus arrhythmia.

The diabetic heart can behave as a denervated heart, with hypersensitivity to catecholamines and a blunted or absent response to beta blockers. It can also be prone to arrhythmias.

Orthostatic hypotension may be produced by autonomic neuropathy in the diabetic. Of interest, orthostatic hypothesion can be initiated or aggravated by the administration of insulin (33), an important fact to remember to avoid confusion with syncope produced by hypoglycemia and to better plan the time of insulin administration in patients with orthostatic hypotension.

Therapy of Heart Disease in Diabetes

Diet, insulin and oral hypoglycemic drugs remain the mainstream of therapy in diabetes.

An atherogenic role of insulin has been proposed, but the issue remains controversial. Tolbutamide has been associated with an increased risk of myocardial infarction and with reduction of left ventricular function. Oral hypoglycemic agents should be reserved for those patients who cannot be controlled on diet alone and who have major difficulties with the use of insulin.

The therapy of cardiomyopathy in diabetes does not differ from the general measures taken in patients without diabetes, with the exception of caution in the use of thiazides and furosemide that may accentuate glucose intolerance by inhibiting insulin release.

The therapy of atherosclerotic heart disease requires some special comments. The most important step is establishing the diagnosis of coronary disease. Diabetics have a particular defect in the pain mechanism. These patients have an increased incidence of severe myocardial ischemia in the absence of angina pectoris and myocardial infarction without pain.

It is well established today that the long term survival in patients with coronary artery disease is determined by the number of coronary arteries with significant obstruction and by the degree of impairment of left ventricular function. Both these parameters can be evaluated by numerous noninvasive diagnostic tests (that is, exercise electrocardiogram, Holter monitoring, radionuclide wall motion studies, etc) and in selected cases by coronary angiography. In patients with diabetes mellitus in whom an evaluation of cardiac prognosis seems appropriate, these methods should be utilized to establish the extent and severity of coronary artery disease.

Once the diagnosis is ascertained, proper medical therapy and, in restricted cases, surgical therapy is commenced. A number of cardiovascular events may thus be prevented or delayed.

The assessment and correction of risk factors for atherosclerosis must also be done rigorously in the diabetic patient. Smoking, hyperlipidemia and hypertension are the most relevant risk factors. When possible, an exercise program may be beneficial in that it is helpful in the correction of metabolic abnormalities as well as in producing cardiovascular conditioning.

The use of drugs in the diabetic patient has some special connotations, that will be addressed in a separate chapter of this symposium.

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Diabetes and Coronary Artery Surgery

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In 1977, two diabetic patients undergoing coronary artery bypass grafting at the Hospital of the Albert Einstein College of Medicine were found to be difficult to wean from cardiopulmonary bypass. General body hypothermia (30°C) and hypothermic (4°C) hyperkalemic cardioplegic ischemic arrest of less than 45 minutes had been used in each case. After rewarming, despite normal serum electrolytes, pCO2, pO2 and pH, and sinus rhythm, effective cardiac contractions, capable of sustaining the circulation, were not present. Inotropic agents were ineffective and increasing the preload as judged by left and right atrial pressures was no help. The blood sugar was in each case high and in each case insulin was given intravenously. Within ten minutes effective myocardial contractions returned and the patients were thereafter quite easily weaned from cardiopulmonary bypass. The temporal relationship between insulin administration and recovery of ventricular function was so striking as to suggest a definite therapeutic effect. In 1978, Muller et al (1) published a description of two cases almost identical to ours and suggested an effect of insulin on ion flux as a mechanism of the beneficial action.

This experience heightened a suspicion that diabetic patients with coronary artery disease were more prone to complications during coronary artery bypass surgery. However, it was not clear to us just what the nature of the difference between diabetics and nondiabetics was and whether such differences that might exist were specific to the presence of diabetes or, rather, related to the presence of more severe vascular pathology in diabetics. A number of questions were raised.

Is the coronary vascular disease more severe in diabetics undergoing surgery for angina?

Is there a special disease of the small vessels in diabetics?

Does diabetes affect the myocardium adversely?

Do diabetic patients respond differently to cardiac surgery?

Is carbohydrate and insulin metabolism adversely affected by cardiopulmonary bypass, surgery and anesthesia?

Does the myocardium of the diabetic respond differently to the circumstances of cardiac surgery?

The Severity of Coronary Disease in Diabetics with Angina

When diabetic and nondiabetic patients with angina are compared, the diabetic patients appear to have more left main disease and more triple vessel disease (2, 3). In Dortimer et al's (2) study of angina patients matched for sex, age, hypertension, lipidemia and smoking history, the difference for coronary score and triple vessel disease were highly significant.

At the macroscopic level, there does not appear to be a difference in the diffuseness of disease in potential surgical patients undergoing cardiac catheterization (2), but in an autopsy study of diabetics compared with age and sex matched control patients (4), there was more diffuseness of coronary disease as well more vessels involved. This difference is probably related to the inevitably selected nature of the patients who are candidates for surgery.

Is There a Special Disease of the Small Vessels?

Although this question is commonly asked, and although arteriolar and capillary microaneurysms have been shown (5), there is in fact no real evidence of the existence of obstructive small vessel disease in the heart. It has not been found in pathologic studies (6) and Barner et al (7) found no difference in vascular responsiveness in flow studies on 461 grafts in diabetics and nondiabetics as judged by systolic and diastolic phasic graft flow and coronary vascular resistance, at the same mean arterial pressure, after 30 seconds

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of graft occlusion and after the injection of 15 mg papaverine into the graft.

Does Diabetes Affect the Myocardium Adversely?

Just as diabetics with angina tend to have more coronary occlusive disease, they are also more likely to have cardiomegaly, diffuse hypokinesis (2) and prior myocardial infarction (8). In patients without extramural coronary disease myocardial changes of severe interstitial fibrosis, focal or confluent scars and extensive myocytolytic activity are seen but only in those who are both hypertensive and diabetic (6). This observation is important to the cardiac surgeon since the combination of hypertension and diabetes occurs often. Our and Muller et al's experience of the beneficial effect of insulin in salvaging four diabetic patients, who otherwise appeared unlikely to survive, is evidence of a different sort of a myocaridal consequence of diabetes.

To put these anecdotal observations into perspective we reviewed, in 1978, the records of 270 patients undergoing coronary bypass surgery in our institution. There were 32 diabetics of whom 15 were on 40 to 80 units per day of NPH insulin, 11 on oral hypoglycemic agents and six were controlled by diet alone. The average data on fasting blood sugar and systolic and diastolic left ventricular function are in Table I. On the average, these ventricles are dilated and have evidence of poor compliance in the form of a raised end diastolic pressure. When compared with nondiabetics randomly picked from the rest of our patients, however, the only difference between the two groups is in the LVEDP, which is significantly higher for the insulin dependent diabetics (Table II). Thus, before surgery, in a group of patients with angina and coronary disease deemed suitable for surgery, those with diabetes appear to have stiffer ventricles. Studies in diabetic dogs with normal extramural coronary arteries have also shown an increased stiffness of the left ventricle. In these dogs, without ischemia, as well as in diabetic humans with coronary disease, an accumulation of interstitial glycoprotein has been seen that may account for the loss of compliance (9).

TABLE I

Thirty-two Diabetics

Average FBS	—	216 ± 16 mg%
Average LV EF	—	63.8 ± 15%
Average LVEDP	—	20.7 ± 6.4 torr
Average EDVI	—	103 ± 36 ml
Average CI	—	2.7 ± 0.7 L/min/m^2

TABLE II

Comparison of Diabetics with Random Nondiabetics

	32 Diabetics	60 Random Nondiabetics
EF	64 ± 15	66 ± 14
EDP	20.7 ± 6.4 (ID-D 22.7 ± 6.3)*	14.1 ± 5.8*
EDVI	103 ± 32	102 ± 32
CI	2.7 ± 0.7	2.9 ± 7

* $p < 0.05$

Do Diabetic Patients Respond Differently to Cardiac Surgery?

The mortality of routine coronary bypass surgery is now so low that it is not a useful index of the response of diabetic patients to surgery. In an attempt to determine whether a genuine difference in response exists, we matched our diabetic patients with a group of nondiabetics with the same left ventricular end diastolic pressure (Table III). The two groups of patients, thus defined, had apparently the same resting left ventricular function. They were operated on by identical techniques using high flow, moderately hypothermic (25−30°C) nonpulsatile perfusion and hypothermic (4°C), hyperkalemic cardiac arrest, and the circumstances of the operation performed also did not differ significantly between the two groups. Despite this, inotropic or mechanical support in the early postbypass period was needed in 45% of the diabetics whereas only 9% of the nondiabetics ($P < 0.05$) required support. Starling curves were obtained in four diabetics and six nondiabetics by measuring the stroke volume index at, at least, three left atrial filling pressures both before bypass, and half an hour after bypass, when hemodynamic conditions were stable. The postoperative levels were depressed compared with the control measurements in four out of four diabetics but were the same or better in five out of six of the nondiabetics. Thus, in our experience, there is evidence of depressed ventricular function early after cardiopulmonary bypass in diabetic patients undergoing coronary artery surgery. This may be due to a difference in the response of

TABLE III

Diabetics and Nondiabetics with matched LVEDP

	Nondiabetics (n33)	Diabetics (n32)
Coronary Score	9.6 ± 2.9	9.8 ± 2.6
No. Grafts	2.3 ± .8	1.93 ± .6
Inotropes/IABP	3 (9%)*	14 (45%)*

* $p < 0.05$

diabetic myocardium to such insults as ischemia and anesthesia or to a different response of glucose and insulin metabolism to cardiopulmonary bypass, anesthesia and surgical trauma.

Is Carbohydrate and Insulin Metabolism Adversely Affected by Cardiopulmonary Bypass, Surgery and Anesthesia?

During cardiopulmonary bypass, there is a rise in blood glucose levels. This occurs even when the perfusate and intravenous solutions do not have added glucose. When operations are performed under hypothermia the initial rise is modest followed by a greater rise during rewarming. The blood sugar remains high during the early postbypass period. Blood insulin levels, by contrast, do not rise and may even fall during bypass. This apparent failure of insulin secretion is particularly evident under hypothermia. Insulin levels become more appropriately high after bypass but when an intravenous glucose tolerance test is performed soon after bypass the insulin response remains blunted. By the next day it has returned to normal. These changes are exaggerated in the diabetic patient (10–12).

There are two phenomena associated with these alterations in insulin and glucose metabolism. During cardiopulmonary bypass, there are marked rises in cortisol, catecholamine and growth hormone levels, with expected consequences on glucose mobilization and production (10, 13). It is also likely that the rise in catecholamine levels inhibits the insulin secretory response to exogenous substrate and the presence of Beta blockade may further depress insulin levels (14). Similar responses have been seen accompanying myocardial infarction (15). Since catecholamine responses are exaggarated under hypothermia, this may account for the more impaired insulin response in hypothermic patients. However, when an attempt is made during hypothermic cardiopulmonary bypass to lower raised blood glucose levels by insulin administration, it is found that the response is minimal. Only after rewarming does insulin begin to produce an appropriate effect (11).

Also, it was shown some time ago that contact of blood with gas in pump oxygenators resulted in alteration in the sulfhydryl group bonding of plasma proteins. Sulfhydryl linkages are vital to the composition of insulin and it is thus not surprising that insulin levels have been shown to fall during *in vitro* circulation through pump oxygenator systems (16).

Does the Diabetic Myocardium Respond Differently to the Circumstances of Cardiac Surgery?

We have already pointed out that there are recognized myocardial consequences of diabetes particularly when hypertension coexists and that these tend to impair ventricular compliance. However, there is also evidence largely derived from studies of diabetic rats and dogs that the hearts of these animals when made ischemic, show earlier and greater impairment of ventricular function than those of nondiabetic controls subjected to the same amount of ischemia. This is only partly related to an impairment of glucose utilization by the myocardial cells (17–19). Since myocardial ischemia is very often present in the course of coronary surgery, the implications for the diabetic patients are obvious.

Summary

The cardiac surgeon must be aware that diabetic patients with coronary disease are in some ways the same and in others different from nondiabetics. By the time they have been through the selection process for surgery, they will not be much different from nondiabetic patients in their pattern of coronary disease. They will, however, be more likely to have hypertension and, when they do, will show evidence of diminished ventricular compliance.

They are more likely to need circulatory support postbypass than nondiabetic patients with the same amount of disease and the same ventricular function preoperatively. The diabetic myocardium handles ischemia less well than that of the nondiabetic. Cardiopulmonary bypass produces hormonal responses and physical effects on plasma proteins that result in high blood glucose and low blood insulin levels, a much diminished insulin response to an intravenous glucose tolerance test and probably a diminished response of blood glucose to insulin administration. These effects are aggravated by hypothermia and worse in diabetics.

Conclusions

The remedy for this situation is not yet clear. The facts do suggest a number of responses for the cardiac surgeon.

A cautious prognosis should be given to the diabetic coronary bypass patients with poor ventricular function. Apart from the greater likelihood that support will be needed postoperatively, the ventricular function and, particularly the compliance, will not necessarily be improved by revascularization.

Pay attention to minimizing ischemic times in the diabetic. It may be an advantage to avoid marked degrees of hypothermia. During surgery, large doses of insulin may be needed to restore ventricular function to an adequate level post-bypass.

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Vascular Disease of the Lower Extremities

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Introduction

Patients with diabetes mellitus have a higher incidence of limb loss than nondiabetic patients because of three major factors which may occur singly or in combination. These include arteriosclerosis obliterans, peripheral neuropathy, and susceptibility to infection. At least in the Western World, the rate of limb loss in diabetic patients with arterial disease is high. Bell, in 1950, (1) reported that approximately half of the gangrene in males and two thirds of that in women was related to diabetes.

An accepted fact is that the atherosclerosis which develops is indistinguishable pathologically from that in nondiabetics but appears to have a different distribution and to be more extensive. For example, in the lower limbs, patients with diabetes have a much greater prevalence of multisegment disease with greater involvement of the medium sized arteries distal to the knee (2, 3).

Of major interest is the question of what factor(s) peculiar to diabetes are responsible for the increased incidence of peripheral atherosclerosis. A major problem in examining risk factors and their relationship to the pathogenesis of the disorder is that only highly selected populations have been tested. It is not clear whether it is possible to define with certainty, the major risk factors involved when only patients with atherosclerosis are tested. Further, not enough attention has been paid to the type of diabetes, its duration and method of treatment employed.

We have conducted a prospective study of the prevalence of arteriosclerosis obliterans in a group of volunteer diabetics who have been studied over a period of four years.

Materials and Methods

Five hundred and twenty volunteers who had been diagnosed as diabetic were evaluated. Each subject was tested for arteriosclerosis obliterans (ASO) by history, physical examination, and noninvasive testing procedures. Additional data gathered on each subject included serum lipoproteins, SMA-12, glycosylated hemoglobin and a 12-hour fasting plasma glucose. In addition, an extensive health history was taken with particular reference to associated complications, life style and medications.

The subjects were divided into six classifications according to the recommendations of the National Diabetes Data Group: 1) IDDM: insulin dependent diabetes mellitus, 2) NIDDM-I: noninsulin dependent for prevention of ketosis but were treated with insulin by their physicans, 3) NIDDM-S: noninsulin dependent treated with sulfonylurea drugs, 4) NIDDM-D: treated with diet alone. (To be included in the analysis, NIDDM-D subjects had to have two annual fasting plasma glucose levels over 140 mg/dl or a single measurement over 200 mg/dl when no second value was available) 5) IGT: impaired glucose tolerance. Those subjects failing the blood sugar criteria for NIDDM-D with a mean of two annual measurements greater than 120 mg/dl (and not on antihyperglycemic medication), 6) Not Diabetic Subjects who failed to fulfill the criteria for the other classification groups listed above.

Each subject was screened for ASO by a combination of three noninvasive tests: 1) resting ankle blood pressure expressed as the ratio of ankle blood pressure/arm blood pressure (normally this is >1.0 but for the purposes of this study, a level of ≥0.95 was used), 2) the ankle blood pressure

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response to exercise (if the ankle systolic pressure fell to 80% or less than baseline and required greater than three minutes to recover, this was considered abnormal), 3) recording of velocity patterns from the arm and leg using a directional continuous wave Doppler system (if the arterial signal was monophasic and above zero, this was considered abnormal). The basis for using these tests and the interpretation has been extensively investigated by previous studies and compared with angiography (4–6).

The data analyzed with regard to the presence or absence of ASO included the following: 1) type of diabetes, 2) age, 3) sex, 4) duration of disease; 5) lipoproteins, 6) fasting plasma glucose, 7) glycosylated hemoglobin, 8) BUN and creatinine, 9) hypertension history, 10) smoking habits, 11) Quetelet's index of obesity (wt/ht^2), and 12) skinfold thickness. The statistical procedures employed included multiple regression, chi-square and the stepwise discriminant analysis from the Statistical Package for the Social Sciences (7, 8).

Results

The distribution, mean age, and duration of diabetes for the six groups are listed in Table I.

Prevalence of ASO

Patients were classified according to four separate diagnostic categories related to the severity of the ASO: 1) segmental disease, those patients with identifiable segments of arterial occlusion, 2) decreased ankle blood pressure, an ankle/arm index of <0.95, 3) an abnormal exercise test and/or ankle pressure, and 4) all detectable ASO based upon abnormal velocity patterns, pressures or exercise. Segmental disease (category 1) is clinically associated with symptoms and complications thus representing the most severe extent of involvement. Detectable ASO (category 4) was found in 34% of the NIDDM subjects and 18% of the IDDM group. The separation by degree of abnormality and disease classification is shown in Table II. It should be noted that the prevalence of ASO is two to three times that noted when only the arteries for segmental disease were used. The lower prevalence in the IDDM group is age related as will be discussed later.

Age, Duration of Diabetes and ASO

For the entire group of diabetic patients using all diagnostic criteria, a regression line has a slope of 7.5% per decade. When only the most severe disease alone is considered, the slope is 4% by decade beginning at age 25. There is no apparent difference in the slope when the NIDDM and IDDM groups are separated but the IDDM patients have a 6.5% greater prevalence of detectable ASO than do the NIDDM subjects of equal age (p = 0.02).

Since the duration of diabetes in the NIDDM group is really not known, it is difficult to draw firm conclusions. However, when all four groups are considered together, there is a slope of 5% per decade (p = 0.04). When a stepwise discriminant analysis is done controlling for age, this relationship persists (p = 0.02). In the NIDDM subjects, 27% who were diagnosed diabetic less than one year have ASO. In the IDDM group, only two of 45 subjects with diabetes less than ten years had ASO.

Sex and ASO

There is an increased prevalence of ASO in males in the NIDDM group ranging from 20%–58% higher. This difference does not appear in the IDDM patients (19% in males, 18% in females). The difference for the NIDDM group is significant (p = 0.009). It should be emphasized that this

TABLE I

Age and Duration of Diabetes

TYPE	NUMBER	MEAN AGE	MEAN AGE AT DIAGNOSIS	MEAN TIME SINCE DIAGNOSIS
Not DM+	41	56	51	5
IGT	23	63	56	6
NIDDM-D	39	59	53	6
NIDDM-S	88	61	53	8
NIDDM-I	162	57	44	12
IDDM	141	34	17	17
	494*			

+ Subjects on multiple antihyperglycemic agents are not included.

* These subjects had been diagnosed as diabetic by their physician at time of entry into the study.

TABLE II

Prevalence of Arteriosclerosis of the Legs in Diabetics by Type of Diabetes, Treatment and Test Criteria

	NOT DM	IGT	NIDDM-D	NIDDM-S	NIDDM-I	IDDM
Segmental Disease	2 (5%)	3 (13%)	8 (21%)	12 (14%)	13 (8%)	9 (8%)
Decreased Ankle BP*	5 (12%)	5 (22%)	13 (33%)	22 (25%)	32 (20%)	17 (12%)
Decreased Ankle BP** and/or Abnormal Exercise	5 (12%)	6 (26%)	15 (38%)	29 (33%)	41 (25%)	23 (16%)
All Detectable ASO*** (Abnormal Ankle BP, Exercise and/or Doppler)	8 (20%)	6 (26%)	16 (41%)	30 (34%)	51 (31%)	26 (18%)
Normal	33 (80%)	17 (74%)	23 (59%)	58 (66%)	111 (69%)	115 (82%)
Total	41	23	39	88	162	141

* Includes subjects with segmental disease

** Includes subjects with decreased ankle blood pressure

*** Includes subjects with decreased ankle blood pressure and/or abnormal exercise

could not be attributed to age differences between the males and females.

Lipoproteins

Overall lipoprotein levels were higher than in an age and sex-adjusted nondiabetic group (Pacific Northwest Bell Telephone Company Health Survey). Cholesterol levels were elevated in all females and HDL cholesterol levels were depressed in the NIDDM-Diet and sulfonylurea treated females. VLDL levels were most elevated in diet treated followed by sulfonylurea treated subjects. However, VLDL levels in insulin treated subjects were not elevated.

When these were related to the prevalence of ASO, different factors appeared for each group: 1) in IDDM and NIDDM-I subjects VLDL triglyceride and LDL cholesterol were important risk factors ($p < 0.01$), 2) no pattern emerged in the NIDDM-S group, and 3) in the NIDDM-D group, the only factor to emerge which was significant was inverse HDL cholesterol ($p < 0.005$).

Hypertension

There was a very high correlation between a history of hypertension and the prevalence of ASO. A regression of detectable ASO with hypertension after controlling for age and sex shows that hypertensive subjects have 19% more detectable ASO ($p < 0.0005$), 15% more decreased ankle systolic pressure ($p < 0.0005$), and 9% more segmental disease than subjects with normal ankle blood pressure ($p = 0.001$).

Also when creatinine levels of greater than 1.2 mg/dl and BUN greater than 21 mg/dl, there was an increased prevalence with an elevated creatinine when all groups were taken together ($p = 0.0182$).

Smoking History

The relationship between a history of cigarette smoking and detectable ASO are shown in Table III. While the differences for each group taken alone failed to reach significance, it was highly significant for the group taken as a whole. For example, in the 49 patients with the most severe (segmental) disease, all but one had been a smoker. In the 96 patients with an abnormal ankle/arm ratio, 78 had smoked (81%) as compared to 219 of 384 (57%) without ASO ($p < 0.00005$).

It is of interest that those who stopped smoking at least two years prior to the study had a 30% lower prevalence of detectable ASO than those who continued to smoke. The prevalence of segmental disease was 19% in current smokers and was 9% in those who had stopped smoking ($p = 0.0206$). This also held true for those with a decreased ankle pressure—32% current smokers versus 20% in those who had stopped smoking ($p = 0.0188$).

Other Variables

There were no positive correlations found between fasting plasma glucose levels, glycosylated hemoglobin or obesity.

TABLE III

Prevalence of Detectable ASO in Diabetic Subjects with and without a History of Smoking

Smoking History	NOT DM	IGT	NIDDM-D	NIDDM-S	NIDDM-I	IDDM	ALL
Yes	5/26 (19.2%)	6/17 (35.3%)	13/25 (52.0%)	25/60 (41.7%)	37/107 (34.6%)	20/73 (27.4%)	108/325 (33.2%)
No	3/15 (20.0%)	0/6 (0%)	3/13 (23.1%)	5/28 (17.9%)	14/55 (25.5%)	6/68 (8.8%)	32/194 (16.5%)
Significance	0.7269	0.2493	0.1717	0.0508	0.3146	0.0087	0.0001

Interaction of Variables

Since correlations between risk factors and ASO may not be direct relationships, a stepwise discriminant analysis was done. It appears that after accounting for the effects of age, sex and type of diabetes, smoking provided an additional 12% increase in the prevalence of ASO ($p < 0.0005$). The results of the discriminant analysis are shown in Table IV. The first column shows that all five variables are statistically significant ($F > 3.84$). When a history of hypertension was accounted for, the importance of age and IDDM decreases somewhat. When age was added to the effect of hypertension, the importance of being an IDDM subject decreased to below significant levels. When smoking was added to the analysis, age and hypertension remain significant but the effect of being male dropped to insignificant levels.

Discussion

There were some expected findings and unanswered questions that emerged from this study. From a prospective study standpoint, it is clear that the type of diabetes and its form of therapy must be taken into account in any analysis of risk factors as related to the prevalence of ASO.

In the NIDDM patients, we really have no information on the duration of the disease. For example it is of interest that 27% of the NIDDM patients had ASO even though they were known to be diabetic for a period of one year or less prior to entering our study. In contrast the duration in the IDDM patients is well known since they require insulin to prevent ketosis. Only two of these patients of 141 with the disease of less than 10 years had detectable ASO.

TABLE IV

Stepwise Discriminant Analysis "F" Statistic on Subjects with/without Detectable ASO

Variables Entered		BP HX+	BP HX+ AGE*	BP HX+ AGE* SMOK HX+
BP HX+	38.60		24.18	22.24
Age*	33.69	19.41		15.98
Smoke HX+	19.32	15.15	11.75	
Male/Female+	7.48	7.64	7.04	3.50
IDDM/NIDDM+	9.92	4.29	1.75	2.28

* Continuous variable

+ Binary variable

With regard to sex and ASO, this has largely been considered a disease of males which appears to be the case in the NIDDM group. However, even here when smoking is taken into account, this difference no longer appears to be significant. There is no sex difference apparent at all in the IDDM patients.

This study also confirms what might have been expected—namely the importance of hypertension and cigarette smoking as risk factors in patients with diabetes. Also, it appears clear that there is a distinct benefit from stopping smoking in the prevalence of ASO. Whether these risk factors are more common or more important in the presence of diabetes cannot be answered since we did not have an age, sex matched control group for comparison.

The issue of diabetes control and complications has been hotly debated. This study did not provide evidence to support any view since our analyses only included fasting plasma glucose and glycosylated hemoglobin levels. Since these cannot be used to predict the blood sugar levels throughout the day, the results of our study should not be unsuspected. This relationship will require the availability of better methods of defining this critically important point.

Finally, it still remains unclear as to what extent diabetes per se contributes to the prevalence of ASO independent of the other risk factors. A key question such as this will be defined only when a control, nondiabetic population is analyzed in a similar fashion.

Summary

The prevalence of arteriosclerosis obliterans was evaluated in 141 insulin-dependent and 289 noninsulin-dependent diabetics and in 64 other subjects. The prevalence of lower limb atherosclerosis ranged from 18% in the younger insulin-dependent group to 41% in those treated by diet.

The prevalence of arterial disease increases 7.5% per decade and is increased 6.5% in the age adjusted insulin-dependent group. It also appears to be increased by 9% in males, 19% in those with hypertension and 12% in smokers. When the effect of smoking is accounted for, the risk for developing arterial disease in the noninsulin-dependent males is not significantly greater than for females. No significant correlations with fasting plasma glucose, glycosylated hemoglobin or obesity were found.

In the insulin-dependent and insulin treated patients, VLDL triglyceride and LDL cholesterol correlated positively with prevalence. In the diet treated patients, only inverse HDL cholesterol correlated with the prevalence of arteriosclerosis obliterans. In the sulfonylurea treated patients, no particular lipoprotein pattern emerged as being significant.

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Cerebral Vascular Disease in the Diabetic

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Unlike the propensity to arterial insufficiency of the legs, the diabetic has less clinically appreciable increased incidence of cerebrovascular disease. Perhaps one of the reasons that the cerebral arteries behave so differently is that protected as they are from external mechanical forces, they are very thin walled for their caliber. There are almost no elastic fibers in the media. The puzzling question is why the cerebral arteries are relatively spared in the diabetic when the retinal arteries are so dramatically involved. As one tries to sift through the epidemiologic literature (1) to document this statement, most reports of stroke, for example, show from a 1.2 (2) to a two-fold increase (3) in the diabetic as compared to the nondiabetic. Such statistics are subject to confusion since the most likely underlying causes of stroke, hypertension and hyperlipidemia are recognizably higher in the diabetic, with probably some unique susceptibility to stroke.

The incidence of diabetes in the general population in the United States is about 4%. Extrapolation from these figures led Bennet (4) to conclude that the probability of developing diabetes in those surviving to age 85 was 23% in the male and 35% in the female. In analyzing our experience (5) in over 400 femoropopliteal bypasses, the incidence of diabetics was 32%. In a similar analysis of 302 patients undergoing carotid endarterectomy, largely for transient ischemic attacks, 21% of the patients were diabetic.

A clinical surgeon often finds a real difference between the diabetic and nondiabetic artery in the legs. When arteriosclerosis occurs in the diabetic, however, it is apt to be more extensive than in the nondiabetic and an endarterectomy sometimes discloses an obliteration of the plane between the media and adventitia (Monckeburg sclerosis) with gritty flecks of adherent calcium, making the task more difficult than usual. Arteriograms of diabetic foot arteries show increased small vessel obliteration. No such differences have been appreciated in the cerebrovascular area. Therefore, the general problem of cerebrovascular insufficiency will be discussed from a surgeon's perspective without further regard to any differences between the diabetic and nondiabetic. Obviously, only some of the high points can be given.

An extensive discussion of diagnostic modalities is beyond the scope of this presentation but some generalities are in order. When the need arises for surgical procedures, such as coronary artery bypass or resection of an aortic aneurysm, in which periods of hypotension may occur, the clinician should attempt to discover and correct any lesions that could lead to an intraoperative or early postoperative stroke. Experience has shown that the common lesion in this category is stenosis of the carotid artery, quite predictably situated in the internal carotid at its junction with the common carotid artery. It is tragic to take the patient through such major surgery successfully only to be confronted with the ravages of a major stroke.

The course is simple if a history of a transient ischemic attack is obtained or a carotid bruit heard. However, the majority of patients with this type of lesion do not give such a history or have a bruit. The physician then must make use of the batteries of noninvasive tests which are available such as measurement of eye pressures by plethysmographic techniques, Doppler flowmeter measurements of blood pressure and direction of flow, and ultrasonic imaging of the

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carotid bifurcation area to mention only the most common. These have more than a 90% yield in discovering significant lesions. Cases are in the courts in which the only ground for malpractice award was the failure to preoperatively study a patient who developed a stroke postoperatively. If such tests point to the probability of a lesion, the present "gold standard" is arteriography. All four arteries to the brain should be visualized. There is much written and said about the definition of a significant lesion. However, it must be remembered that there is great inherent difficulty in trying to base three dimensional judgments on two dimensional x-rays. A large ulcerated placque can be missed completely or the degree of stenosis grossly underestimated if the plane of the x-ray does not match the plane of the lesion. It is almost a rule that the pathology encountered at the operating table is much greater than that seen on the film.

A word of caution is in order: give thought to the route through which the catheter is to pass. The femoral artery in the groin is by far the most common choice but should be avoided if there is arterial insufficiency of that leg or if the catheter would have to pass through an aortic aneurysm with the attendant danger of dislodging an intramural thrombus. The alternate route is through the axillary artery. If this is selected, be sure the arm pulses are normal beforehand. These decisions must be shared with, but not relinquished to the radiologist.

By way of perspective, it is virtually certain that in the near future the noninvasive testing and the need for arteriography via a Seldinger catheter will be largely replaced by the availability of high quality intravenous arteriography which will be as innocuous as an intravenous pyelogram is today. Prototype x-ray machines are already in use which simultaneously sum multiple fluoroscopic images and subtract bony structures. Fact will be arrived at easily and controversy about the extent of workup will disappear.

Do not depend on the presence or nature of a bruit to herald carotid pathology. Ulceration most often is not associated with a bruit. The natural history of a progressive stenosis is first, absence of a bruit, then gradual increase in intensity, gradual decrease in intensity, and disappearance.

There is great controversy concerning the proper treatment for the asymptomatic patient with a carotid bruit and even for the patient who has had a single episode of amaurosis fugax for a fleeting mini-stroke (TIA). The sides are sometimes quite predictable, with the neurologist and internist on the side of antiplatelet aggregation drugs while the vascular surgeon usually opts for surgical intervention. Admittedly biased, we strongly feel that the patient should undergo arteriography under any circumstance. If a stenosis or ulceration is demonstrated, surgical therapy is clearly indicated. This is based on a very low incidence of morbidity and essentially no mortality in carotid surgery as opposed to the number of patients who go on to stroke within a year or two if they have not had known lesions corrected. Part of the controversy was fueled by the Veteran's Administration Cooperative Study which showed that although the nonsurgically treated patients had a higher stroke rate, this was offset by the higher incidence of mortality and morbidity in the group which was treated surgically. As is always a concomitant of this type of cooperative study, it was carried out in a wide range of hospitals with highly variable surgical statistics. Where there is access to a vascular surgical service of top quality, the surgery should be done.

Still another area of heated controversy is whether the TIA is caused by a transient decrease in blood flow or is due to small emboli arising from ulcerated placques. The answer is, as you might expect—both. Typical patients are frequently seen in whom high grade stenosis occurs in the absence of ulceration and vice versa.

Let us now assume that a symptomatic patient has been demonstrated to have a significant lesion in the carotid artery. If the lesion and the symptoms match, then the decision for surgery is relatively easy. On the other hand, a goodly number of patients have been seen who have had no further symptoms after carotid surgery in whom the symptoms were on the same side as the carotid lesion or the symptoms were assumed to be in the posterior circulation and yet there was no demonstrable pathology in the vertebral-basilar complex. What must be remembered is flow through the circle of Willis and the various communicating arteries within the cerebral circulation, can lead to various "steal" situations in which blood is siphoned from one area to another. Another decision which must be made is when to operate on the patient who has had more than a transient ischemic attack. For purposes of discussion, let us assume a patient who has been plegic for a day or so and has some residual weakness. The sooner the patient is operated upon the less the risk of another similar episode or the occurrence of a full fledged stroke. The fear of doing immediate surgery is that of converting an ischemic to a hemorrhagic infarct. The difficulty of this decision has been eased by the availability of the CAT scan. If this shows an infarct, surgery should be delayed four to six weeks; if not, it is safe to go right ahead.

Still another situation that can make for difficult decisions is the common finding of bilateral carotid stenosis. Which side should be done first? This decision should be predicated on the dynamics of the cerebral flow shown on the arteriogram. If the flow is predominantly from one side to the other, the recipient side should be done first. What if there is no shunting from one side to the other? Then the side of the non-dominant hemisphere should be done initially. This last rule is sometimes not followed. For example, in a right handed man with a 95% stenosis of the left carotid and a 60% stenosis on the right, it is recommended that the left side be done first because this will cause the least deprivation of perfusion during the inevitable interruption of blood flow.

Once the decision has been made to augment the carotid circulation by surgery, what operations are available? By far the most common is carotid endarterectomy. Here the carotid artery is opened, the offending arteriosclerotic placque (often a core) removed, and the artery closed with or without a patch of vein or prosthetic cloth to widen it. Unhappily, if the internal carotid is closed completely, it cannot be reopened because it will have thrombosed up to the internal carotid in the brain just before the origin of the middle cerebral artery. In this situation, the other carotid should be repaired if it is stenotic. If not, the external carotid is almost always patent. One of its branches, the superficial temporal artery can be anastomosed directly to a tributary of the middle cerebral artery complex on the surface of the brain. This is called a temporo-middle cerebral bypass. This is a most useful procedure in the rare case in which it is indicated. However, it takes about six weeks for the small branch of the middle cerebral artery to enlarge enough to supply maximal additional blood flow. Frequently, it is necessary to correct a stenosis in the external carotid artery at its origin in order to assure adequate inflow for the temporomiddle cerebral bypass.

Again, it is beyond the scope of this presentation to go into the many operative details of carotid artery reconstruction. These include the choice of anesthesia, either local or general, and the use of shunt during endarterectomy to provide the brain with blood flow during the time of repair. If this type of surgery is done in a hyperbaric chamber at 3 atmospheres absolute, the need for a shunt is obviated because the pO^2 of arterial blood goes to about 1800 and the venous return with the carotid cross clamped remains arterialized (6).

The use of the hyperbaric chamber is basic to a new project on the treatment of the acute stroke. By way of background, the acute stroke caused by sudden arterial occlusion has not been treated surgically because of the fear of converting an ischemic to a hemorrhagic infarct. When patients with acute strokes are subjected to hyperbaric oxygenation within six to eight hours of onset, 30% will recover immediately. Because oxygen is toxic, such therapy is unsafe for more than two to three hours at a time. The stroke recurs as soon as the oxygen tension is lowered. With the second treatment, only half of the patients show recovery and, with the third treatment, none. Both the surgical and hyperbaric approaches then have been disheartening, but the two approaches can be put together. The hypothesis is that if the patient recovers when under hyperbaric oxygen, there is no infarct present. Here is a method to select out the reversible cases and immediately proceed with surgery while under pressure. Only two such cases have been done but these have been most encouraging.

While carotid lesions are by far the most common problem that the surgeon is called upon to treat, vertebral arterial insufficiency certainly deserves some exposition.

Most stenoses of the vertebral artery occur at the point of its origin from the subclavian artery. An obstructive arteriosclerotic placque is the usual cause but very frequently the obstruction is caused by elongation and kinking of the artery itself, secondary to fixation by surrounding connective tissue. Both conditions are easily corrected by the experienced vascular surgeon. In the case of the arteriosclerotic placque, endarterectomy is the usual choice with or without the application of a prosthetic patch to widen the artery. Division and reimplantation of the vertebral artery into the adjacent carotid artery is also useful at times.

Sometimes, the vertebral artery becomes compressed as it runs up its bony canal within the vertebral foramina. The diagnosis of this entity is suggested by a history of syncope which occurs when the neck is turned in one direction or another. Arteriography often reveals a bony spur that occludes the vertebral artery when the neck is in one particular position. Such lesions are corrected by removing the offending bony spur.

Of more physiologic fascination is the "subclavian steal syndrome." In this entity, the subclavian artery is stenotic just proximal to the takeoff of the vertebral artery. As a result, the affected vertebral artery and the distal subclavian artery have a decreased arterial pressure. The affected vertebral artery communicated with the opposite vertebral and two carotid arteries, all at normal arterial pressure, through the circle of Willis. Blood thus flows in a retrograde direction down the vertebral artery and out into the arm via the subclavian artery. Thus, blood flow is "stolen" from the brain to supply the arm.

The standard corrective surgery has been a bypass from the adjacent carotid to the subclavian artery to restore normal arterial pressure in the subclavian-vertebral arterial system. In recent years, an alternate procedure has become more popular (7). This consists of bypassing from one axillary artery to the other, thus restoring normal pressure in the subclavian-vertebral system without occluding the carotid artery, an unavoidable maneuver in the carotid subclavian bypass.

Because of the current popularity of the technique of intraluminal dilatation, conceived by Dotter but improved and popularized by Gruntzig, a comment is in order. If an area of stenosis or a short constriction is discovered in an artery it has been found practical to pass a very strong deflated balloon into the area and then inflate the balloon under high pressure so as to compact the arteriosclerotic placque, much as one pushes the snow to the side of a driveway. The experience thus far has been quite satisfactory in the coronary, renal, and iliac arteries, and less satisfactory in the superficial femoral arteries. This technique, however, has not been used in the carotid or vertebral arteries. The reason for this is the likelihood of dislodging adherent clot on the wall of the artery or spilling out debris from a subintimal placque, with immediate embolization to the brain. A good new tool, but contraindicated in the cerebral circulation until diagnostic methods improve to the point of being able to select which lesions are safe to approach in this way.

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The Heterogeneous Response to Exercise in Diabetes Mellitus

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When required, diet, exercise and hypoglycemic agents (oral agents or insulin) are the cornerstones of diabetes treatment. Of these, the role of exercise is probably the least understood and certainly the most imprecisely utilized. This has in great part been related to our poor understanding of the abnormal metabolic responses observed in diabetics. In addition to improving metabolic control in diabetes, exercise may independently correct other risk factors important in the progression of atherosclerosis (1). These include a lowering of very low density lipoprotein and low density lipoprotein, while increasing circulating high density lipoprotein. Other beneficial effects are an increase in maximal oxygen uptake, lowered blood pressure, enlarged coronary artery lumen, increased cardiac output, and increased physical work capacity. As well, exercise can promote weight loss and has been shown to increase insulin sensitivity.

Since atherosclerosis occurs with increased frequency in diabetic populations, the importance of an exercise program in the management of these patients is emphasized.

To effectively utilize exercise in the treatment of diabetes, a more precise understanding of the metabolic responses of diabetics as compared to normals is required. Recently, acute and chronic studies in diabetic man and animals have provided new insights into the pathophysiologic responses observed.

We will review the results of studies undertaken to examine the effect of diabetics under differing metabolic and nutritional states. We will develop the hypothesis that insulin plays a critical role in ensuring a normal response to exercise and demonstrate the consequences of abnormal insulin regulation in diabetes.

Responses to Exercise in Insulin Dependent Diabetes

Considering the complexity of fuel fluxes during exercise and the important regulatory role of hormones (particularly insulin) in mediating the metabolic response, it is not surprising that diabetics respond to exercise differently than normals do. This is not evident in diabetics receiving exogenous insulin, since insulin "release" in these patients is entirely unphysiologic. Varying states of insulin deficiency or excess may occur which influence the metabolic response to exercise. To examine the role of abnormal insulin regulation in exercise it is helpful to divide the studies performed into three subgroups: a) studies performed after varying periods of insulin withdrawal, b) studies in close temporal relation to subcutaneous depot insulin injection, and c) studies in which insulin was administered by constant intravenous infusion during exercise.

Exercise after Insulin Withdrawal

The metabolic response to exercise in diabetic man withdrawn from insulin is in great part determined by the severity of insulin deprivation. Studies performed 16–24 hr after the last administered dose of insulin are descriptive of differing metabolic states (2). In severely insulin deficient, ketotic diabetics exercise results in an exacerbation of the ketosis and an increase in glycemia (3). However, with less severe insulin lack, either no change or a fall in glycemia has been shown to occur with exercise. Since plasma insulin concentrations have not been measured in most studies, it is not possible to relate these responses to systematic changes in insulinemia. However, as de-

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scribed below, it appears that this is an important factor since absorption of residual depot insulin can be accelerated during muscular contractions, and resting state hyperinsulinemia is encountered both in insulin treated diabetes and in the obese noninsulin dependent diabetics.

An appropriate model for studying the effect of insulin deprivation on exercise in which most variables can be controlled is the depancreatized dog. Unlike human studies, the possibility of residual islet cell function is eliminated, and the measurement of IRI is not hindered by the presence of insulin antibodies.

Using the technique of primed tracer glucose infusion for measuring glucose turnover, depancreatized dogs were subjected to exercise after a short period of insulin withdrawal (4). The dogs were initially maintained normoglycemic by an intraportal infusion of insulin that was then discontinued during a subsequent 60 min rest, 75 min exercise and 75 min postexercise period (Fig. 1). Plasma IRI remained measurable but at low levels of 5−8 μU/ml. During the insulin infusion, steady state normoglycemia was obtained. The infusion of tracer maintained constant specific activity and concentration of labelled glucose in the plasma. Upon termination of the insulin infusion, plasma glucose started to rise and the specific activity of glucose decreased, reflecting increased glucose production. The plasma concentration of 14C glucose increased, corresponding to a reduction in the metabolic clearance of glucose. The utilization of glucose, however, did not decrease because the increasing glucose concentration in plasma compensated through a mass effect for the fall in its metabolic clearance. When exercise was initiated, marked hyperglycemia with accelerated glucose production resulted. Though glucose uptake increased in proportion to plasma glucose concentration, this rise was much less than that seen in normal dogs. Expressing the glucose uptake data in terms of the metabolic clearance,

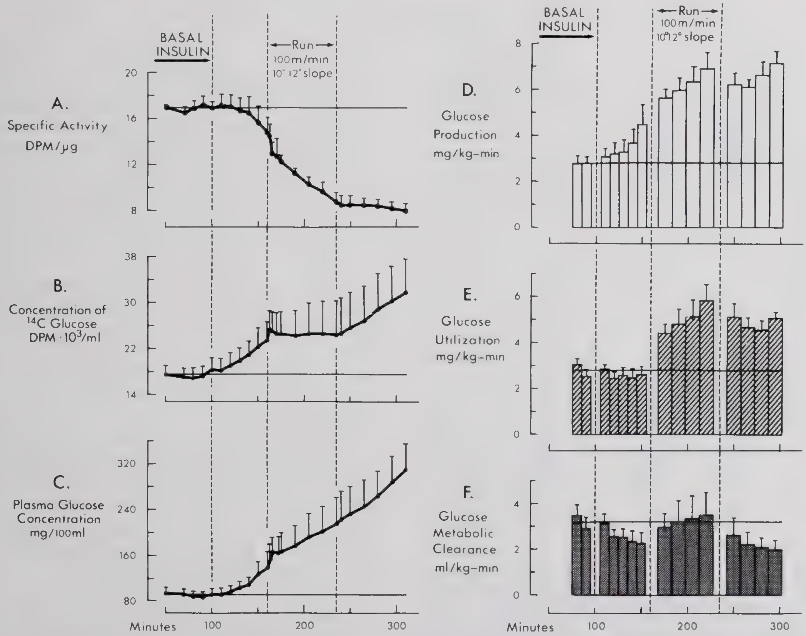

FIG. 1. Glucose turnover by the method of primed tracer infusion (14C glucose). The effects of insulin withdrawal and exercise in five depancreatized dogs on (A) specific activity of 14C-glucose and (B) plasma levels of 14C-glucose, (C) unlabeled glucose, (D) the rates of glucose production, (E) rate of glucose utilization and (F) metabolic clearance of glucose. Plasma levels and turnover of glucose were maintained near normal during the initial 100 min of rest by a basal infusion of insulin. The insulin infusion was discontinued thereafter and the experiment was continued for an additional 60-min rest, 75-min exercise and 75-min post-exercise period in the complete absence of insulin. Reproduced from Vranic et al, 1976 (4).

which in part adjusts for the changes in glycemia, demonstrates more clearly the defect in muscle glucose utilization, that is, metabolic clearance was essentially unchanged. Thus, exercise promotes glucose utilization effectively only when an adequate, albeit small, amount of insulin is present. Otherwise, exercise has an adverse effect because the increase in glucose production exceeds that of utilization, resulting in further hyperglycemia.

Exercise after Subcutaneous Depot Insulin Injection

The metabolic response to exercise in diabetics receiving subcutaneous insulin reflects either a state of insulin deficiency or excess at the onset, followed by a more consistent excess during or after exercise. This phenomenon appears to be mediated at least in part by enhanced depot insulin absorption. Again, the accelerated absorption was clearly demonstrated in the depancreatized dog model (Fig. 2), this time 7 hrs after subcutaneous protamine zinc insulin injection (5). Studies in man (Fig. 3) have demonstrated that hypoglycemia presumably due to accelerated depot insulin absorption during exercise is particularly prominent when the site of insulin injection is an actively exercising extremity (6, 7). In Figure 4, the plasma IRI concentration in nondiabetic normals is compared with that of two diabetic subjects (without insulin antibodies) receiving intermediate acting insulin subcutaneously in the thigh 1 hr prior to 45 min of moderate bicycle exercise. In contrast to the significant fall in IRI measured in normal subjects during exercise, a two-to-four-fold increase was demonstrated in the diabetic subjects.

The consequences of this elevation in IRI on glucoregulation are illustrated in Figure 5. In normal subjects, glycemia remains constant during exercise since glucose production and glucose

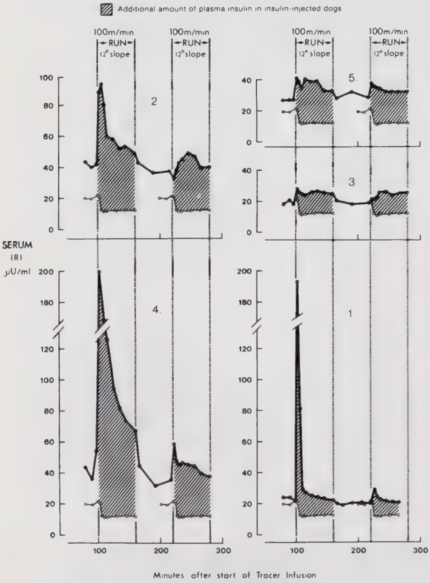

FIG. 2. Serum concentration of IRI during rest and exercise in five depancreatized dogs 8–9 hours after administration of foods and insulin. Shaded areas designate the differences between individual IRI levels in each depancreatized dog, and mean levels of IRI in five normal dogs. Numbers identify each dog. In each depancreatized dog, IRI increased during exercise and all exercise IRI values were higher than in normal dogs. In all these dogs, exercise induced a normal increase in glucose utilization, but increases in glucose production were only marginal. Reproduced from Kawamori and Vranic, 1977 (5).

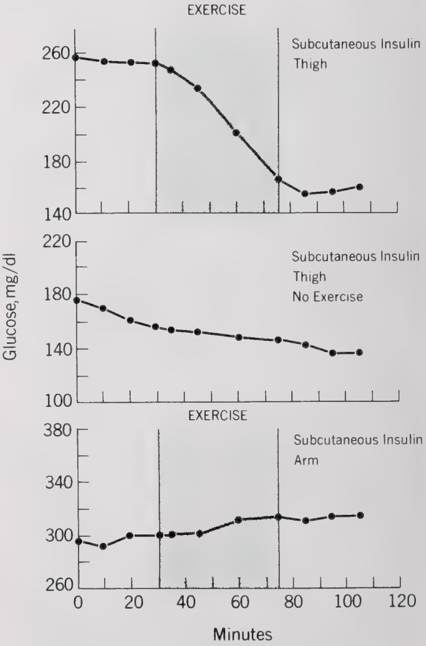

FIG. 3. Plasma glucose response to bicycle exercise and varying sites of subcutaneous administration of insulin. Reproduced from Zinman et al, 1977 (6).

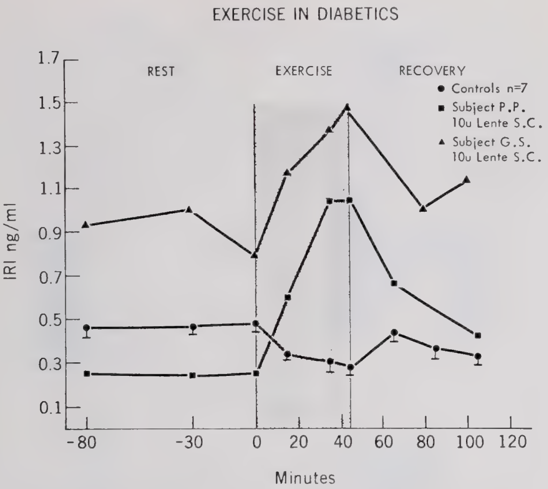

FIG. 4. Serum immunoreactive insulin at rest, during exercise and recovery in normal controls and two diabetic subjects. Reproduced from Zinman et al, 1977 (6).

utilization increase in a synchronous manner. The increase in hepatic glucose production is facilitated by the fall in IRI, but the IRI concentrations remained at a sufficient level to allow for the exercise induced increase in muscle glucose uptake. The basis for the fall in glycemia in the subcutaneous insulin treated diabetics with exercise is apparent in Figure 5.

Hepatic glucose production was elevated at rest (Fig. 5 S.C.) reflecting insulin deficiency. The abnormal fall in glucose production with exercise was presumably the result of the elevated IRI inhibiting hepatic glucose production, while on the other hand muscle glucose utilization increased normally.

The rise in IRI with exercise predictably affects the concentration of other circulating metabolites. As is evident in Figure 6, the increase in IRI during exercise in the diabetic subjects resulted in a failure of FFA to rise normally, presumably mediated by its antilipolytic effect. The smaller increase in glycerol during exercise in these subjects also supports this observation. As well, the normal post-exercise increase in 3-hydroxybutyrate was attenuated. Since the rate of hepatic ketone body production is determined by the provision of FFA substrate and the ketogenic capacity of the liver (8, 9); this observation is consistent with a decreased presentation of FFA to the liver with or without an altered rate of ketogenesis.

Thus, the metabolic response to exercise in diabetics receiving subcutaneous insulin may be affected by abnormal excursions of plasma insulin, resulting in disturbed glucoregulation and a failure of adequate energy substrate mobilization. Certain therapeutic implications can be drawn from these observations with regard to exercise induced hypoglycemia. The appropriate selection of insulin injection sites and the alterations in diet in anticipation of exercise are two possible therapeutic modalities for preventing exercise induced hypoglycemia. On the other hand, exercise induced improvement of hyperglycemia is desirable when plasma glucose does not decline below normal levels.

Exercise during Constant Insulin Infusion

The metabolic response to exercise in diabetics receiving a constant insulin infusion was examined to further define the role of insulin during exercise. These studies may have relevance to mechanical devices designed to control glycemia by intravenous insulin delivery (portable insulin infusion pumps). Interestingly, when diabetic subjects are maintained either normoglycemic or hyperglycemic by a constant continuous periph-

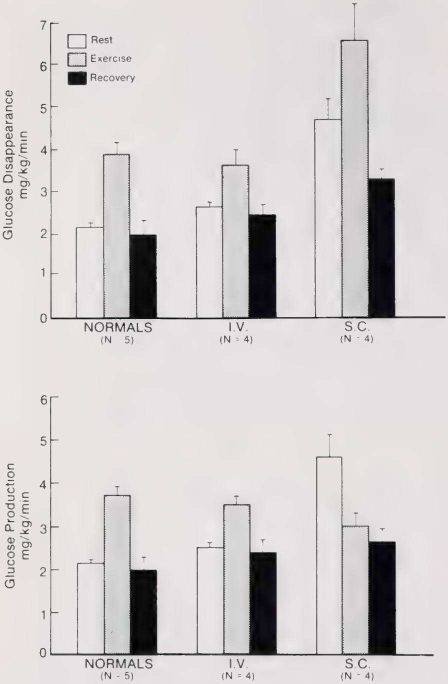

FIG. 5. Effect of exercise on glucose turnover. Glucose utilization (upper panel) and glucose production (lower panel) at rest and after 45 minutes of exercise for the normal controls and the insulin-infused (i.v.) and subcutaneous (s.c.) insulin-treated diabetics. Reproduced from Zinman et al, 1979 (19).

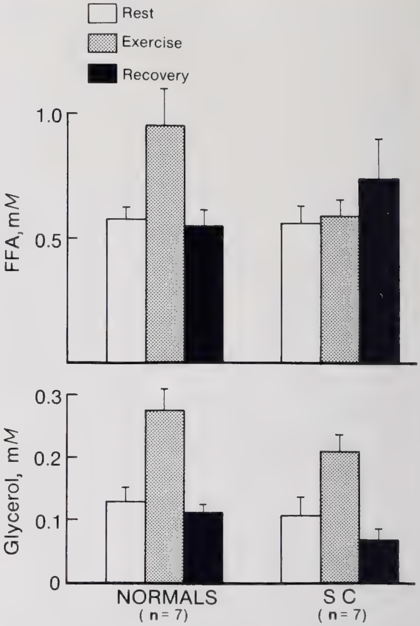

FIG. 6. Plasma free fatty acid (FFA), and blood glycerol concentrations in seven normal controls and seven diabetic subjects receiving subcutaneous insulin (S.C.) 1 hr prior to exercise at rest, after 45 min of exercise and 60 min recovery. Reproduced from Zinman et al, 1979 (14).

eral intravenous insulin infusion, glucose production and glucose disappearance increase synchronously with exercise and glycemia remains unchanged (Fig. 7). This observation corresponds to that in depancreatized dogs maintained normoglycemic by a constant intraportal insulin infusion (4). These studies imply that a decrease in insulin delivery in the postabsorptive state is not essential for a normal glycemic response to exercise.

The above discussion of the role of insulin in mediating the glucoregulatory response to exercise is summarized schematically in Figure 8. The effect of normal insulin dynamics on hepatic glucose production and muscle glucose utilization are contrasted with the consequences of insulin deprivation and hyperinsulinemia.

Responses to Exercise in Noninsulin Dependent Diabetics

Although the metabolic consequences of acute exercise in insulin treated diabetes has been extensively studied, the effect of exercise on diabetics not requiring insulin has received less attention. Since this group comprises the greater portion of diabetics, exercise as a potential modality for treatment requires further exploration. One such study is summarized as follows. To compare glucoregulation during moderate exercise, obese diabetics and similarly obese nondiabetic controls were exercised in the postabsorptive state for 45 min on a cycle ergometer at 50% of their estimated maximum oxygen consumption (10). One half of the diabetics were treated with diet and chlorpropamide and the other half were treated with diet alone. All were hyperglycemic in the postabsorptive state. The response to exercise was similar in both diabetic groups. As illustrated in

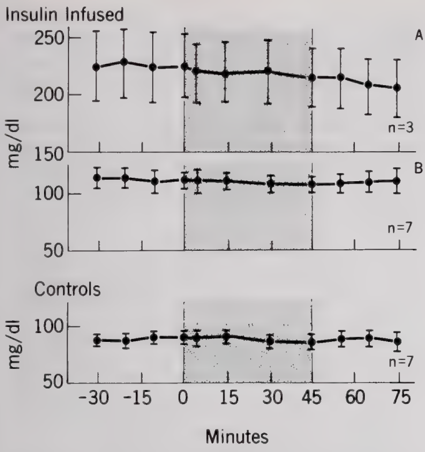

Fig. 7. Plasma glucose response to exercise (shaded area) in diabetics maintained either (A) hyperglycemic or (B) normoglycemic by constant intravenous infusion as compared to normal controls. Reproduced from Zinman et al, 1979 (6).

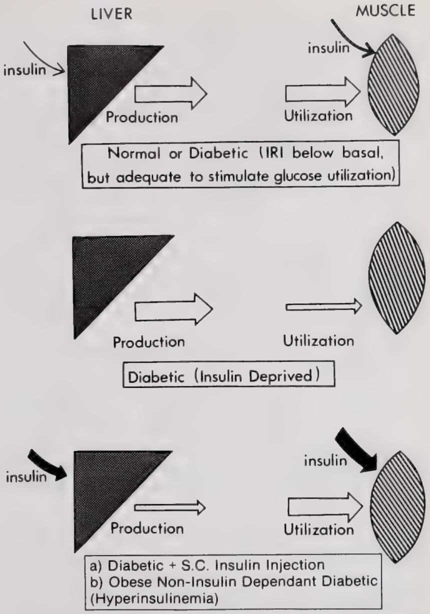
LIVER
MUSCLE
insulin
insulin
Production
Utilization
Normal or Diabetic (IRI below basal, but adequate to stimulate glucose utilization)
Production
Utilization
Diabetic (Insulin Deprived)
insulin
insulin
Production
Utilization
a) Diabetic + S.C. Insulin Injection
b) Obese Non-Insulin Dependant Diabetic
(Hyperinsulinemia)

Fig. 8. The role of insulin in mediating hepatic glucose production and muscle glucose utilization in a state of normal insulinemia, insulin deprivation and hyperinsulinemia. (Reproduced from Vranic and Berger (20).

Figure 9, exercise results in a significant decrease in glycemia in the diabetics while no change occurred in the obese controls. The decline in glycemia was due to a failure of hepatic glucose production to rise during exercise concurrent with the increase in muscle glucose disappearance. Although the IRI concentration decreased with exercise as expected in the obese controls, no change was observed in the IRI concentration of the diabetic subjects. It is thus possible that the sustained insulin concentrations observed with exercise in the diabetic subjects were responsible for the failure of hepatic glucose production to increase (Fig. 8). It is generally accepted that the normal fall in IRI during exercise is mediated by sympathetic activity. The observation described above suggests that such sympathetic control of insulin secretion is abnormal in obese diabetics. Alternatively, it is possible that hyperglycemia was causing near maximal stimulation of B cells, not suppressible by adrenergic activation. The inhibiting effect on hepatic glucose production is probably a result of the continued effect of hyperinsulinemia and hyperglycemia itself because studies in animals (11, 12) and man (13) have shown that hyperglycemia per se can limit hepatic glucose production.

Irrespective of the precise mechanism, this study indicates that exercise in addition to diet can play a role in improving glycemia in obese non-insulin dependent diabetics. The effects of long-term exercise programs on glycemic control will more clearly establish the importance of exercise as a therapeutic modality. The significance of exercise programs is further emphasized by the notion that exercise can increase the affinity of insulin to its receptors (14).

The Effect of Exercise Training in Diabetes Mellitus

Much less information is available on the effects of exercise training in diabetes. Several studies have suggested that exercise programs in these diabetics result in enhanced insulin sensitivity (15, 16). Saltin demonstrated improved oral glucose tolerance despite unchanging insulin levels in normal weight diabetics with abnormal glucose tolerance after three months of physical training (17). Although Bjorntorp was not able to demonstrate improved oral glucose tolerance in

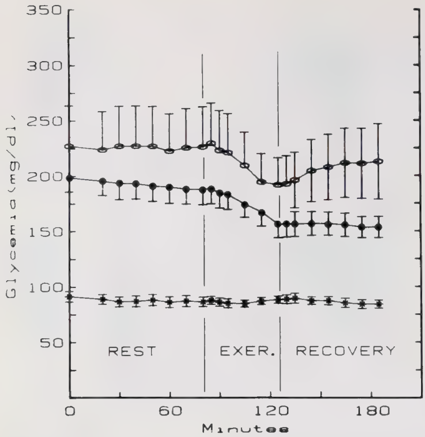

Fig. 9. The effect of exercise on plasma glucose (mean ± SEM) in obese controls (x), obese diabetics treated with diet alone (●—●) and obese diabetics treated with diet and chlorpropamide (○). Reproduced from Minuk et al (10).

five obese non insulin-dependent diabetic subjects undergoing an eight-week exercise program, he did demonstrate a lowered fasting level of insulin, suggesting increased insulin sensitivity (15). A short duration of the effect of training on insulin sensitivity was reported by Ruderman (18) who found that two weeks after maturity onset diabetics stopped training, fasting glucose and insulin levels tended to increase and glucose tolerance had decreased significantly.

Summary

The abnormal metabolic response to exercise in insulin dependent diabetes mellitus can in great part be related to abnormal insulin levels. Exercise during insulin deprivation results in an increase in glycemia (because of deficient muscle glucose uptake) and ketosis. Exercise shortly after subcutaneous depot insulin administration results in hyperinsulinemia due to accelerated depot insulin absorption. The elevated insulin inhibits hepatic glucose production and FFA mobilization from adipose tissue. When insulin is given by constant intravenous infusion during exercise, the glucoregulatory response is normal. Exercise in obese diabetics not requiring insulin also shows difference from normal with respect to insulin and glucoregulation. Unlike normal controls, exercise in these diabetics results in a reduction toward normal in glycemia due to a much lesser increase in hepatic glucose production as compared to controls. This effect may be mediated by the sustained levels of insulin seen during exercise in these subjects.

A more precise understanding of the metabolic responses to exercise will enable the attainment of the ultimate goal, namely defining a specific exercise prescription in the treatment of diabetes mellitus.

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Hyperglycemia, Including Oral Hypoglycemic Agents

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Hyperglycemia is the pivotal diagnostic measure of impaired glucose tolerance and diabetes mellitus. In these states atherosclerosis occurs prematurely and in higher prevalence than in the nondiabetic population (1–5). The degree of glucose intolerance has been directly related in several studies to the prevalence of atherosclerotic disease, groups with borderline glucose concentration manifesting a prevalence rate midway between the control group and the increased rate observed in frank diabetes mellitus (6). In other surveys (7–9), the finding of blood sugar elevations following a glucose challenge has been much higher in patients with diagnosed atherosclerosis than in the normal population. Viewed in terms of blood glucose concentrations, it would appear that a direct relationship exists between the prevalence of atherosclerotic disease and glucose intolerance, possibly further related to the severity of the latter.

While this relationship may be a valid one, a causal role for hyperglycemia per se in atherosclerosis has not been established. Nor has the correction of hyperglycemia with current methods of treatment using insulin or sulfonylurea been shown to reduce the prevalence of macrovascular disease of diabetes. A recent report (10) reveals no correlation between progression of the atherosclerotic disease and the duration or severity of diabetes mellitus. Persistent hyperglycemia, regardless of its cause, is associated with a number of metabolic and biological alterations which are acknowledged risk factors in atherogenesis. This susceptibility to atherosclerosis observed in diabetic patients involves not only the influence of hyperglycemia but also such concomitant aberrations as lipid abnormalities (11), blood clotting and platelet disturbance (12, 13), osmotic and rheologic alterations affecting blood flow, glycosylation of circulating and structural proteins (14), increased polyol pathway activity and microvascular abnormalities. Even hypertension in diabetic patients, a prominent risk factor (15, 16), may be related directly or indirectly to hyperglycemia since a return to normotension has been observed in patients whose blood glucose has returned to normal during periods of continuous subcutaneous insulin infusion. Although improvement in these diabetes-related abnormalities can be achieved by sophisticated methods of treatment, conventional management of diabetes has not been shown to influence macrovascular disease in diabetes. This is particularly evident in the female diabetic patient in whom both coronary artery disease and nonatherosclerotic lesions of intramural coronary branches occur at a rate far in excess of her nondiabetic counterpart (16).

It will be important to determine if prolonged periods of glucose regulation will reduce the incidence of arteriosclerosis with the use of constant insulin infusion pump, islet cell transplantation or other methods being studied for the correction of metabolic abnormalities of diabetes. Increased concentrations of blood glucose appear to enhance the vulnerability of the diabetic patient to atherosclerosis through interactions with other risk factors. Hyperglycemia alone has not been found to be a serious risk factor in the Framingham data. Nevertheless, the increased incidence of cardiovascular disease among otherwise healthy hyperglycemic subjects in the Bedford and Tecumseh studies suggest that hyperglycemia is a precursor of atherosclerotic disorders. The prevalence of hypertension among patients with diabetes has not been explained although studies have demonstrated that insulin causes sodium retention in diabetic patients (17) and augments sodium absorption in diabetic rat kidneys (18).

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Most investigators have shown that hypertension increases the risk of atherosclerosis among diabetics. (9, 15) Predisposition to atherosclerosis in the diabetic has been related to hyperlipidemia which in turn is correlated with hyperglycemia although other factors such as diet, genetic factors, and adiposity play an important role. Numerous reports implicate hyperlipidemia, regardless of etiology, as a frequent finding among diabetic patients with atherosclerosis. Adiposity is a common concomitant but its role as a risk factor in the absence of other risk factors including hyperglycemia is unclear. In the Framingham study, diabetic women with coronary artery disease demonstrated a high frequency of hypertriglyceridemia, obesity and low HDL cholesterol (4). Studies on survivors of myocardial infarction manifest abnormal glucose kinetics during the first six weeks in 36 to 85% of cases reported in various series (19–21). Similar incidences of hyperglycemia are reported in patients with occlusive vascular disease of lower extremities (22, 23) suggesting that it is not myocardial infarction that produces glucose intolerance but that the vascular disease is related to an excessive prevalence of glycemic abnormality. It is of interest that in primitive populations, the incidence of diabetes may increase during periods of environmental change but the incidence of atherosclerotic disease increases only after the appearance of other risk factors such as hypertension and hyperlipidemia. (24)

Indirect support for the notion that hyperglycemia per se is not a potent risk factor is found in the low frequency of coronary artery disease in the Pima Indians although microangiopathy is frequently seen in this diabetes-prone population (25). In South Africa the studies of Campbell demonstrate increased vascular disorders among Natal Indians compared to Blacks in these diabetic populations consuming similar diets (26). Long term studies by Merrimee (27) of sexual ateliotic diabetic dwarfs, an isolated growth hormone deficiency state, demonstrate a relative freedom from atherosclerosis in these patients. Thus the complex nature of atherosclerosis occurring prematurely in the diabetic and obliterating the usual gender differences appears to involve the predisposition to vascular damage imposed by hyperglycemia accelerated or activated by concomitant risk factors, predominately hyperlipidemia, smoking and hypertension. Genetic and hormonal factors are also involved in this intricate equation.

If hyperglycemia and its associated abnormalities are indeed responsible for the increased prevalence of atherosclerosis in the diabetic patient, can this condition be altered by treatment of the diabetes? The challenge of prevention of long-term complications of diabetes has defied students of this disease for many decades. Within recent years data have accumulated to support the concept that careful regulation of blood glucose can provide benefits in terms of the microvascular disorders associated with diabetes. In experimental diabetes and in clinical studies, neuropathic abnormalities, glomerular lesions and the retinal alterations have been shown to improve with treatment programs designed to provide effective control of plasma glucose concentrations (28). Whether similar programs for glycemic control can produce comparable results for diabetic patients with arteriosclerotic disease cannot be answered at the present time.

A central issue in diabetes is the diversity of its pathogenesis. A variety of mechanisms are recognized in the heterogeneous types of diabetes for the development of atherosclerosis (29). In the Type I diabetic patient, insulin deficiency deprives the individual of the essential triglyceride clearing activity of lipoprotein lipase leading to accumulation of atherogenic lipoproteins and a reduction in HDL. On the other hand, the Type II diabetic patient manifests insulin resistance with basal and stimulatory hyperinsulinemia which increases hepatic lipoprotein production in conjunction with a defect in clearance. Dietary factors have been intensively studied with variable results. Current interest is focused on the high carbohydrate, high fiber diet which has reduced plasma glucose, serum cholesterol and triglyceride concentrations permitting discontinuance or a reduction in dosage of insulin and sulfonylurea in a significant number of patients (30, 31). Clinical and epidemiologic studies indicate that diet and states of insulin deprivation and insulin excess associated with hyperglycemia are important contributing elements in macrovascular disease.

An effort to find a solution to the effect of various types of treatment upon the chronic complications of diabetes was initiated in 1960 by the UGDP (32, 33). This multicentered program was designed to test and to compare the effectiveness of five therapeutic schedules in adult diabetic patients with respect to the appearance or progression of vascular and neurological manifestations observed in this population. Among the groups of patients were a total of 1027 who were randomly assigned initially to four treatment schedules including placebo and diet alone (PLBO); Tolbutamide (TOLB), 5 gm TID; fixed insulin dosage (ISTD) based on body weight; and variable insulin dose (IVAR) adjusted on basis of fasting blood glucose; a fifth group was added receiving phenformin (PHEN), 50 mg BID (34). Cardiovascular mortality reported in this study demonstrated a disproportionate incidence in patients receiving oral antidiabetic therapy, both tolbutamide and, subsequently, phenformin. The study showed that control of blood glucose, achieved most effectively in the IVAR dose program, did not influence mortality from established atherosclerosis over a five-year period. The summarized data from which these conclusions were drawn showed a cardiovascular mortality of 12.7% each for tolbutamide and phenformin contrasted to 4.9%, 6.2%, and 5.9% for placebo, fixed insulin, and variable insulin treatment, respectively.

Termination of the tolbutamide treated group was effected at the end of eight years because of an inordinate rate of cardiovascular mortality among these patients; the phenformin group, started 18 months after the initiation of the study, was also discontinued with an identical cardiovascular mortality each being more than double the cardiovascular mortality in any other group (34). While the explanation for this increased mortality was not clear, subsequent studies (35, 36) suggested an increased inotropic effect of the agents. Presumably, enhanced inotropism induced by tolbutamide resulted in myocardial infarction or fatal arrhythmia in the presence of coronary artery disease. Although an inotropic effect of tolbutamide was demonstrated by Lassiter and Levy (35) using a rabbit cardiac muscle preparation, subsequent investigation by Lucchesi (37) and others (38) did not confirm this finding. Additional research has suggested that the inotropic effect may be species specific and, based on noninvasive studies in humans, was not applicable to humans in whom no significant effect was observed.

Related to this issue was a report from Great Britain (39) showing an increased incidence of tachyarrhythmia in sulfonylurea treated patients compared to insulin or diet treated patients admitted to several hospitals with myocardial infarctions. A number of criticisms leveled at the paper led to a similar study in the U.S.A. In the latter multicenter study (40), there were no significant differences in the incidence of tachyarrhythmias among the three groups of patients—sulfonylurea, insulin or diet treatment—following admission to acute care facilities. Similar findings were reported by Clark (41).

More recent studies have compared the responses of HDL cholesterol in patients receiving sulfonylurea treatment to those receiving insulin. Diabetic patients have been found to have low HDL concentrations under conditions of poor control. With insulin treatment HDL 2 and HDL 3 have been increased to normal, while VLDL and TG are lowered by such treatment. Several contradictory reports (42—45) have emerged concerning the effect of sulfonylurea. Bar-on (42) found lower levels of HDL cholesterol in patients treated with sulfonylurea while Paisey (44) found no significant difference in HDL values after twelve months of treatment. Further studies on the response of HDL 2 and the associated apoproteins to sulfonylurea therapy are awaited with interest because of the inverse correlation between HDL and atherosclerosis, the levels of HDL being lower in patients with coronary artery disease than in matched controls. Among normal subjects, the relative protection of women compared with men may be related to higher HDL found in females, an effect apparently related to estrogens which increase VLDL and HDL concentrations while androgens have the opposite effect.

Following the publication of the UGDP report, a number of authorities voiced serious disagreement with the assertion that the sulfonylurea agents or biguanides were responsible for an increase in cardiovascular mortality. Prospective studies of less intricate design were published by Keen (Bedford Survey) (46), by Paasikivi, Stockholm (47), and by Feldman (Kaiser-Permanente study (48) which showed similar mortality rates in placebo and sulfonylurea treated patients. Other prospective investigations and retrospective analyses of cardiovascular mortality involving groups of patients treated with insulin, sulfonylurea or diet failed to support the UGDP results (49—53). Thus, the influence of tolbutamide on atherosclerotic processes, whether beneficial or adverse, is inconclusive and inconsistent with the disparate reports probably due to patient selection.

Standardized management of other precursors of atherosclerosis was not included in the design of the UGDP study although certain clinical features such as vascular disease, history of cardiac disorder, and hypercholesterolemia were part of the baseline analysis. Participants consisted of widely heterogeneous groups of older diabetics in whom the precursors of macrovascular disease were only partially evaluated and remained unattended even when recognized. Because of this, neither the relative significance of separate risk factors nor the benefits of intervention are addressed in this study.

Among the main criticisms leveled at the UGDP study were the following: the apparently inadvertent inclusion of patients with multiple risk factors in the tolbutamide group: improper treatment of many patients using fixed doses of tolbutamide, INST or phenformin; assignment of deaths to the original treatment group of patients who died on different treatment or dropped out of the group; half of the cardiovascular deaths occurred in two of the twelve clinical centers while in four other centers, no cardiovascular deaths occurred; autopsy rates were 25% in the groups other than tolbutamide for which the rate was 50%. One of the principal investigators at the St. Louis center of the UGDP, Kilo, with access to computer records of the study, showed that there was a spuriously low cardio-vascular mortality in the placebo group (54) which flawed the statistical base (55) and that exclusion of patients who changed medication or dropped out virtually confined the excessive cardiovascular mortality in the tolbutamide group to those with fasting blood sugar greater than 200 mg/dl. Analysis of cardiovascular mortality in those with fasting blood sugar below 200 mg/dl revealed similar rates for tolbutamide and both insulin treated groups. With correction for risk factors such as hypertension and persistent hyperglycemia, the cardiovascular deaths among IVAR treated patients was reduced to three indicating that proper administration of insulin was effective in reducing cardiovascular mortality. The conclusion of the analyses published by Kilo and Williamson (54) is that the UGDP study demonstrates beneficial effects derived from blood glucose control in both TOLB and IVAR groups compared to PLBO controls when the data are corrected for other cardiovascular risk factors. The initial controversy aroused by the report led to the hiring of the Biometric Society for a review of the statistical analysis of the UGDP data (56). The committee assigned to this task by the Society did not have access to the original data and found that the statistical evaluations appeared valid. A similar conclusion was reached following an internal audit of the data by a committee appointed by the FDA (57). Recently, both the ADA and the AMA have issued new policy statements following further investigations of the current status of the UGDP. These statements encourage a reexamination of the purported cardiotoxic role of sulfonylurea agents and advise physicians to use their own judgement concerning appropriate methods for management of patients with diabetes.

Conclusions

Hyperglycemia, the basic diagnostic criterion for impaired glucose tolerance and diabetes mellitus, is related to atherosclerosis as a risk factor predisposing to vascular pathology. The nature of the precursor role of elevated blood glucose is not clear but it appears to augment the atherogenic effects of other risk factors of recognized importance in the general population such as hypertension, hyperlipidemia and smoking. In the presence of hyperglycemia, these risk factors and others related to the diabetic state including aberrant insulin levels, blood clotting abnormalities, osmotic and blood flow perturbations are associated with a doubling of the prevalence of atherosclerosis.

Although the UGDP report demonstrated an increased incidence of cardiovascular deaths in patients receiving tolbutamide, there have been sharp divisions of opinion concerning its acceptance as an indictment of the sulfonylurea drugs. The conclusions reached in the study become increasingly untenable with lack of confirmation. Irrespective of the outcome of this controversy, the problem of retarding atherosclerosis in diabetes remains a complex problem requiring a multiphasic approach including dietary adjustments, control of hypertension and improved methods for long term treatment which will correct plasma lipid and glucose abnormalities.

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Journal

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The Mount Sinai Hospital: Success in the Competition for Survival

SAMUEL DAVIS*

In New York and five other states, hospital revenue has been capped. As a result, these states now have inflationary rates far lower than the national average. The success of this experience suggests that capping income would be an appropriate way to control national hospital inflation.

An Historical Overview

To understand how the hospital industry got into a highly inflationary position, we will first take a look at the industry's recent history.

From 1945 to 1960, health care policy was essentially laissez-faire. Most of a hospital's revenue came from the private sector—a combination of patient fees and philanthropy.

The major infusion of federal money at the time was the Hill-Burton program, developed by Congress to provide capital for hospital construction and renovation. In exchange, hospitals were required to give a set amount of free services to the poor.

In the 1960's, the Kennedy and Johnson Administrations made a bold promise to the country by calling health care a right of all Americans. Five federal programs drastically changed the way hospitals did business: *Medicare*—for the elderly, administered by the federal government through local fiscal intermediaries; *Medicaid*—a state administered program for the poor, supported half by the federal government and the rest by states or a combination of state and local resources; *Regional Medical Programs*—an attempt to get the knowledge that was in medical schools distributed to local hospitals in their areas; *Comprehensive Health Planning*—state-run programs designed to make sense out of the local allocation of resources; and *Community Mental Health Centers*—a commitment to provide psychiatric services to anybody who needed them.

These programs increased public sector spending more than seven times between 1965–1980. The cost of Medicare alone is still doubling every 4 years—from $9 billion in 1972, $18 billion in 1976, to $34 billion in 1980.

In the 70's, with Gerald Ford and Jimmy Carter, we began to see proposals for limits to growth. For the first time, since World War II, we began to hear: we can't afford it . . . let's cap it . . . let's not spend anymore. A series of legislative and regulatory actions were developed to attempt to control the rate of increase of health care costs. In the 70's, we saw wage and price controls . . . Medicare limits on physician fees and on allowable hospital costs . . . the development of PSRO's . . . and a Certificate of Need process.

This was the period during which the Club of Rome issued its paper on limits to growth. This was when, in 1973, we had our first energy crisis. It was a period when suddenly Americans began to look at themselves and say, we can't afford to do everything. This attitude was felt first and most dramatically in health care services in six states that began to regulate hospital revenues, one of which was New York.

The Mount Sinai Profile

Hospital patient revenue comes from four sources: *Medicare,* which reimburses hospitals for what they spend to provide services; *commercial insurance carriers* that pay the prices set by hospitals for their services; and *Blue Cross and Medicaid,* which in New York State reimburse hospitals on a flat prospective daily rate for all patients, regardless of the care they receive.

In New York, the office of Health Systems Management develops the formula by which Blue Cross and Medicaid pay hospitals. In an effort to control costs, the state placed an average 9% inflationary cap on expenditures during a time that

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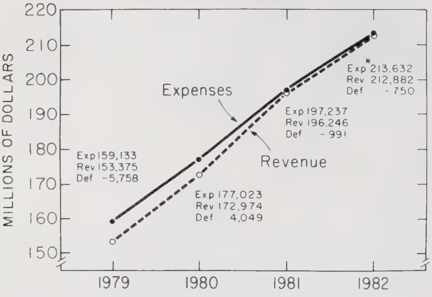
* President, The Mount Sinai Hospital; Chairman and Edmond A. Guggenheim Professor, Department of Health Care Management, Mount Sinai School of Medicine of The City University of New York, NY.

EXHIBIT A

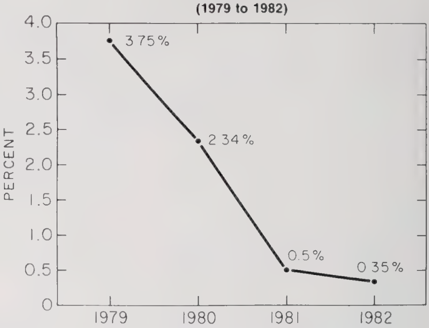
THE MOUNT SINAI HOSPITAL
REVENUE, EXPENSES, AND DEFICIT
(1979 to 1982)



* Net of $597 unallocated expense reductions

EXHIBIT B

THE MOUNT SINAI HOSPITAL
DEFICIT AS PERCENT OF REVENUE
(1979 to 1982)



the national hospital inflation rate averaged 15% per year.

These financial restraints have posed a major challenge to New York hospitals. Over 6,000 beds and 17 institutions have closed. Some hospitals that we are familiar with no longer exist as we once knew them and have merged.

Other institutions, like Mount Sinai, took these controls as an opportunity to manage hospital operations more efficiently. In 1979, with revenue of $153 million, Mount Sinai had a deficit of almost $6 million. In 1982, with revenue of $212 million, we expect to close the gap and achieve a pure break-even position (Exhibit A).

During this time, the deficit as a percentage of revenue dropped dramatically, from 3.75 percent in 1979 to .35 percent in 1982 (Exhibit B). Contributions as a percentage of total expenses remained almost constant: .8 percent in 1979, .9 percent in 1982 (Exhibit C).

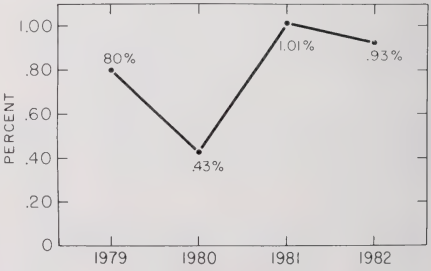
This record was accomplished at the same time we increased direct patient care services. In 1981, there were 300 more "hands on" nurses than there were in 1977. In 1982, we plan to have 100 more than we had in 1981. Nursing manhours have increased from 34 to 39 percent of the total hospital manhours. (Exhibit D). In addition, we have added roughly 17 more to our house staff and brought on 90 new staff to enhance our clinical programs.

The money to achieve this record came from what those in the hotel business call the back of the house: housekeeping, food service, medical records, engineering, all the support activities. Support staff has been reduced to 48 percent of our total hospital manhours (Exhibit A).

We achieved our results through a carefully orchestrated productivity improvement program. First, we conducted an audit of labor-intensive departments of the hospital, looking for target areas where we could make substantial cuts. We then developed a quality control mechanism to make sure that what we would cut would not adversely affect patient services. Each of our senior managers was given targets. The job was difficult. There were no home-runs; it took a series of sin-

EXHIBIT C

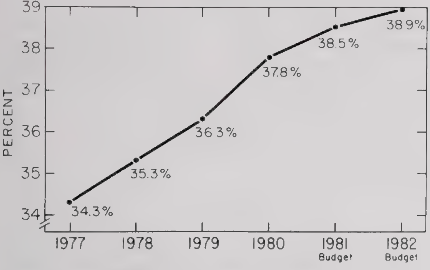
THE MOUNT SINAI HOSPITAL
BUDGET PROCESS
CONTRIBUTIONS AS % OF TOTAL EXPENSES
(000 omitted)



	CONTRIBUTIONS	EXPENSES	%
1979	1,278	159,133	80
1980	762	177,023	43
1981	2,000	197,237	1.01 Budget
1982	2,000	214,229	93 Budget

EXHIBIT D

THE MOUNT SINAI HOSPITAL
NURSING HOURS AS A PERCENTAGE OF TOTAL HOURS
(1977 to 1982)



Year	NURSING DEPT. %	NURSING DEPT. Hours	TOTAL HOSPITAL HOURS
1977	34.3	3,328,261	9,705,280
1978	35.3	3,519,283	9,960,620
1979	36.3	3,654,781	10,056,583
1980	37.8	3,814,031	10,086,863
1981	38.5	4,009,917	10,409,251 Budget
1982	38.9	4,205,765	10,820,536 Budget

This schedule includes an allocation for Private Duty Nurse Hours

gles to win the game. And the game took five years to play. Once we got to the staffing level with which we were satisfied, we developed a tool to monitor productivity—a manpower reporting system that identified every cost center in the hospital by hours worked, hours paid, dollars budgeted, dollars paid. With this data base, we are able to monitor past and present performance and make rational decisions to increase or decrease resources where needed. We can now review all of our departments by units of activity. For example, we can measure housekeeping by square footage cleaned, food service by number of meals prepared and delivered. The productivity program is part of a new management approach at Mount Sinai.

The Health Care Policy of the Future

Few hospitals in the country have been through the vigorous productivity improvement programs that Mount Sinai and some of the other institutions in the six regulated states have put in practice. As a result, hospital costs have far outstripped the general rate of inflation in the economy.

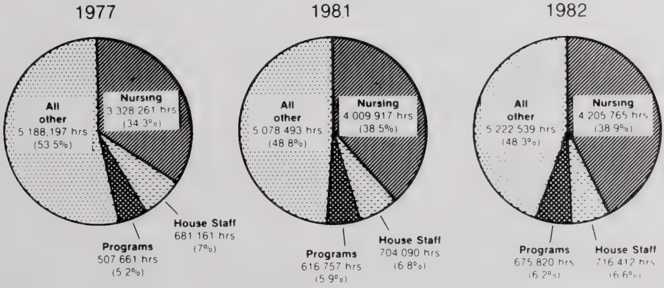
Health care now takes up ten percent of our country's resources. The Reagan administration has made clear that the country must restrain further increases in expenditures, and keep health costs at about ten percent of the gross national product. How we restrain the growth is now a major public policy issue. Let's take a look at what could be done.

We could cut the supply of hospitals and physicians and let the patient queue be a determinant as it is in Britain. If you're really sick, you get treated; but if it's elective surgery, you get in line . . . you wait to have a hernia repaired . . . to have a gall bladder taken out.

Another possibility is to raise the price in the market place and let laissez-faire economics ration for you, or develop a two-class system: economy and first-class. Those who have an economy ticket will get basic services, and those who can afford it, can have additional services.

EXHIBIT E

THE MOUNT SINAI HOSPITAL
COMPARISON OF 1977-1981 AND 1982 HOURS



We could develop a policy that denies access to certain age groups, as in the Soviet Union, where people over the age of eighty-five are denied admission to intensive care units.

Another possibility is to develop informed consumers, people who know what they're buying in the market place. Do for the general population what Dr. Spock did for mothers many years ago—enable them to know how to get access to medical care when they need it.

We could establish competition in the market place—have insurers and providers compete for the consumer's dollars.

But the country is not ready for changing our current approach to the delivery of health care. Business, unions, and the insurance industry have pressured the administration to pull back on its competition proposals. The sophistication of consumers is not at the point at which we can have consumer-driven market competition. And the other alternatives require a major change in our philosophical approach to health care—changes that require political courage which the country is not ready for.

The one option that is available, that has proven results, is the regulation of income. I believe that in the near term, hospitals across the country will be moving into a selective Darwinian environment—in which hospitals are tested for the survival of the fittest (similar to the experience in the six regulated states).

This movement provides a new set of challenges for the industry. To survive, hospitals are going to have to define their mission, to identify what they are, and what's important. They've got to cut their losers, or convert them into winners. They've got to get productive. They've got to begin "organizational restructuring."

Hospitals will be going into businesses that they would never have contemplated years ago; nursing homes, pharmacies, shopping malls, a variety of activities to generate cash flow to support the basic business.

Medical schools are going to have to go through the same rigorous rethinking. It's no accident that Massachusetts General Hospital recently signed an agreement with a large drug firm that has great income-generating potential. It's no accident that Mount Sinai is looking carefully at what kind of resources are in our patent bank today and what kind of opportunities there are tomorrow.

Physicians will have to look at other options . . . new forms of group practices, like HMO's, or relocation to areas that might not have been thought about years ago. HMO's have not taken off in the New York area, but in other places around the country they are really working well. In Minneapolis-St. Paul, for instance, thirty percent of the population are covered by HMO's.

1984 and Beyond

With income regulation as the basic tool to reduce costs in the near term, hospitals will have to develop strategic planning efforts, start productivity improvement programs, and find new ways to restructure their system. We can expect more consortia . . . more mergers . . . more vertically linked systems under voluntary auspices . . . and more horizontally linked systems in the for profit sector.

Through 1984, the end of this administration's first term, there will still be enough fat in the system to keep hospital costs down by regulating income.

After 1984, proposals for competition—among insurers, among doctors, among hospitals—may emerge again. For academic medical institutions such as ours, there is a major problem in the competition approach: will the consumer have the ability to differentiate among different kinds of providers, that is, the quality of services of a small community hospital versus the quality of services of a major teaching institution such as Mount Sinai. If all hospitals are to compete with each other on an equal basis, the only equitable method would be to remove the educational component from a teaching hospital's costs. Segregating educational from service costs will be difficult. And when the costs are broken out, how the educational component will be funded will be a major policy issue.

Mount Sinai's management has played a leadership role in establishing ways to control costs in a regulated income system of reimbursement. We will continue to be in the forefront—to anticipate change, and plan for the Hospital to flourish—as new approaches to controlling costs are developed.

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Studies in Pancreatic Function VII. Diabetes, Exocrine Pancreatic Function and Pancreatic Disease*

DAVID A. DREILING, M.D., HUGO GRATERON, M.D., NEIL FINKLER, B.S., GUILLERMO CARBONELL, M.D., AND ORLANDO BORDALO, M.D.

There is a considerable amount of literature concerning the relationship between diabetes, exocrine pancreatic secretion, and pancreatic disease—a relationship emphasizing interaction between endocrine and exocrine function. The occurrence of diabetes and disturbed carbohydrate tolerance in exocrine pancreatic disorders is partially understood and has been generally accepted to be the result of involvement of α and β islet cells by the pathology in the surrounding exocrine parenchyma. Concerning the occurrence of pancreatic parenchymal involvement and pancreatic secretory dysfunction in various diabetic states, there is marked disagreement in the literature with observations varying from the absence of exocrine disease and secretory defect to frequent association of diabetes and pancreatic deficiency (1–7). Additional confusion has been added by numerous reports of pharmacologic, if not physiologic actions, of the various "APUD" polypeptides, the enkepholins, and peptinergic mechanisms which call attention to rather complicated feedback mechanisms between the endocrine and exocrine moieties of the pancreas.

This report is a retrospective study: 1) of patients with exocrine pancreatic disease evincing diabetes and 2) of patients with diabetes associated with exocrine pancreatic disorder and dysfunction.

Materials and Methods

Clinical data was drawn from 1151 cases reviewed from a total of over 15,000 patients subjected to the secretin test in the Pancreatic Diagnostic Laboratory. The following groups were established:

1. Normal controls: 123 patients
2. Adult onset diabetes: 202 patients
3. Juvenile diabetes: 52 patients
4. Chronic pancreatitis with diabetes: 124 patients
   Chronic pancreatitis without diabetes: 91
5. Pancreatic cancer with diabetes: 106 patients
   Pancreatic cancer without diabetes: 152 patients
6. Biliary tract disease with diabetes: 91 patients
   Biliary tract disease without diabetes: 224 patients
7. Cirrhosis: 66 patients

In all patients, pancreatic secretion was assessed using the standard secretin test technique, that is, an intravenous bolus stimulus, 1.0 units/kg, and a collection period of 80 minutes (8). The parameters studied were:

1. flow—range 2.0–4.0 ml/kg/80 min
2. maximum bicarbonate concentration—range 90–130 mEq/L
3. enzyme secretion—8.3–21.5 u/kg/80 min amylase.

The data were interpreted according to the following patterns of secretion:

1. total deficiency—decreased flow, maximum bicarbonate concentration and amylase secretion
2. quantitative deficiency—decreased flow
3. qualitative deficiency—decreased maximum bicarbonate concentration
4. isolated enzyme deficiency—decreased amylase secretion
5. hypersecretion—increased flow

From the Pancreatic Research Laboratory, the Department of Surgery, Mount Sinai School of Medicine (CUNY) and the Hospital Santa Maria, Lisbon, Portugal.

* Supported in part by a grant from the Alfred and Florence Gross Research Fund.

Requests for reprints should be sent to Dr. David Dreiling, Mount Sinai School of Medicine, One Gustave L. Levy Pl., New York, NY 10029.

TABLE I

Mean Secretin Test Data of 594 Diabetics Studied Compared to 123 Controls

	#	X ± S.E. Volume ml/kg	$\bar{X}$ ± S.E. Max (HCO_3) mEq/L	$\bar{X}$ ± S.E. Amylase μ/kg
Normal Control	123	3.2 ± .04	107 ± 0.7	14.9 ± 0.29
Diabetics	594	3.1 ± .09	89 ± 1.2	16.1 ± 0.50
Normal Range		2.0 – 4.0	90 – 137	8.3 – 21.5
P Value		>0.5	<.001	>0.4

Biochemical analyses included serum enzymologic determinations (amylase), blood sugars, glucose tolerance tests, and routine blood chemistries.

Diagnoses were confirmed in all cases by radiologic, endoscopic, surgical and other morphologic techniques necessary.

Statistical analysis was performed using the Student "T" Test. Only probabilities less than 5% were considered significant.

Results

Table I presents the secretin test data of all the diabetic patients (594) and compares the findings with those observed in the controls (123). There was no significant difference between the average rates of flow and amylase secretion following secretin. The observed average maximum bicarbonate concentration of the diabetics, 89, is significantly less than in controls, 107, but is close to the lower limit in the normal range of 90 mEq/L. Thirty-seven percent of all the diabetic patients exhibited abnormal secretory patterns. The secretin test data of patients with Juvenile and Adult onset diabetes is given in Table II. The observations of each group are compared with controls as well as with each other. The flow and bicarbonate data do not differ. The rate of amylase secretion of the patients with adult diabetes is statistically significantly increased over controls. Comparison of the Juvenile Secretory data with controls reveals no difference in amylase secretion. Flow and maximum bicarbonate concentrations, however, are statistically, significantly lower. Indeed, the mean maximum bicarbonate of juvenile diabetics falls below the normal range. Finally, when the adult and juvenile diabetic groups are compared to each other, statistically significant differences are seen for all three parameters. The rates of flow and amylase secretion as well as the maximum bicarbonate concentrations following secretin are less in juvenile than in adult onset diabetes. In 60% of the juvenile diabetics, the secretory pattern was abnormal compared with adult onset diabetes where the incidence of abnormal secretion was 13%.

The pancreatic secretion findings of 215 patients with chronic pancreatitis are summarized in Table III. Ninety percent of the patients had alcohol associated disease. The data are presented in two groups, those with and without concomitant diabetes. It is clear that the average flow, maximum bicarbonate concentrations, and amylase secretions following secretin are less in the diabetic than the nondiabetic group. The data are statistically significant for bicarbonate and amylase. Only bicarbonate values fall below the normal range.

The secretin test data of pancreatic cancer patients with and without diabetes is analyzed in Table IV. Average flow, bicarbonate and amylase secretion in response to secretin is less for the patients with diabetes but only the maximum

TABLE II

Mean Secretin Test Data of 202 Adult Onset Diabetic and 52 Juvenile Diabetics Comparison is Made Between These Two Groups and for Each Group with Controls

	#	$\bar{X}$ ± S.E. Volume ml/kg	$\bar{X}$ ± S.E. Max. (HCO_3) mEq/L	$\bar{X}$ ± S.E. Amylase μ/kg
Adult Diabetes	202	3.3 ± .07	111 ± 0.90	20.1 ± 0.70
Juvenile Diabetes	52	2.6 ± .16	78 ± 2.5	12.7 ± 1.8
Controls	123	3.2 ± .04	107 ± 0.74	14.9 ± 0.29
Normal Range		2.0 – 4.0	90 – 137	8.3 – 21.5
P_1 Adult Diabetes vs Controls		>0.5	>0.20	<0.01
P_2 Juvenile Diabetes vs Controls		<0.01	<0.001	>0.10
P_3 Adult vs Juvenile Diabetes		<0.001	<0.001	<0.001

TABLE III

Mean Secretin Test Data of Patients with Chronic Pancreatitis Grouped According to the Presence (124) or Absence of Diabetes (91)

	#	$\bar{X} \pm$ S.E. Volume ml/kg	$\bar{X} \pm$ S.E. Max. (HCO_3) mEq/L	$\bar{X} \pm$ S.E. Amylase μ/kg
Chronic Pancreatitis No Diabetes	91	2.8 ± 0.14	62 ± 1.4	13.3 ± 1.53
Chronic Pancreatitis with Diabetes	124	2.5 ± 0.12	56 ± 1.8	9.1 ± 0.90
Normal Range		2.0 – 4.0	90 – 137	8.3 – 21.5
p		$p > 0.2$	<0.05	<0.02

bicarbonate data are statistically significant. The flow response for both groups of pancreatic cancer is less than the normal range. In the patients with diabetes, the bicarbonate and enzyme secretion is also decreased below the lower limit of normal.

Table V summarizes the secretin test data of patients with chronic cholecystitis and cholelithiasis with and without diabetes. The findings are compared to the data of normal controls. No differences were observed between control subjects and patients with chronic cholecystitis without diabetes. If diabetes was present, the maximum bicarbonate concentration after secretin was statistically significantly lower than in control patients. The same statistically significant difference for maximum bicarbonate can be observed comparing gallbladder disease patients with and without diabetes. The data in all secretory parameters in this group of patients fall within the normal range.

Table VI, presents the secretin test data of 66 patients with diabetes, cirrhosis, and chronic pancreatitis. The data are not analyzed statistically because 1) the numbers in each group are small, 2) the type of cirrhosis varies, 3) and the degree of pancreatic inflammation in patients with cirrhosis is difficult to assess. Indeed, the alterations in pancreatic secretion induced by fibroses involving both liver and pancreas may be opposite in direction, that is, liver cirrhoses augment whereas pancreatic fibroses diminish.

Discussion

Interpretation of the data should attempt to resolve two questions:

1. How does diabetes affect the external pancreatic secretion?

2. How does disease of the exocrine pancreatic parenchyma affect carbohydrate metabolism?

The simplistic answers from an analysis of the data would be:

1. There is a high incidence of abnormal pancreatic exocrine secretion with or without identifiable exocrine pathology in patients with diabetes.

2. Pancreatic inflammatory and neoplastic disease is associated with a high incidence of diabetes.

Why then the wide discrepancies in the literature, differences ranging from

1. Diabetes, per se, has little effect on pancreatic exocrine secretion (1, 2).

2. Diabetes is associated with a high incidence of pancreatic enzyme deficiency (3, 7).

TABLE IV

Mean Secretin Test Data of Patients with Pancreatic Cancer Grouped According to the Presence (106) or Absence (152) of Diabetes

	#	$\bar{X} \pm$ S.E. Volume ml/kg	$\bar{X} \pm$ S.E. Max (HCO_3) mEq/L	$\bar{X} \pm$ S.E. Amylase μ/kg
Pancreatic Cancer No Diabetes	152	1.5 ± .05	97 ± 1.2	8.3 ± .42
Pancreatic Cancer with Diabetes	106	1.3 ± .06	80 ± 2.5	7.6 ± .60
Normal Range		2.0 ± 4.0	90 – 137	8.3 – 21.5
p_1		>0.05	<0.001	>0.5

TABLE V

Mean Secretin Test Data of Patients with Gall Bladder Disease (Chronic Choleciptitis and Cholelithiasis) Grouped According to the Presence (91) or Absence (123) of Diabetes

	#	$\bar{X}$ ± S.E. Volume	$\bar{X}$ ± S.E. Max (HCO$_3$) mEq/L	$\bar{X}$ ± S.E. Amylase μ/kg
G.B. Disease No Diabetes	224	3.3 ± .03	110 ± 1.3	12.9 ± 2.3
G.B. Disease with Diabetes	91	3.4 ± .10	98 ± 2.1	14.7 ± 1.3
Controls	123	3.2 ± .04	107 ± .7	14.9 ± .29
Normal/Range		2.0 – 4.0	90 – 137	8.3 – 21.5
p_1 G.B. No Diabetes vs Controls		>0.2	>0.5	>0.1
p_2 G.B. with Diabetes vs Controls		>0.1	<0.01	>0.1
p_3 No Diabetes vs Diabetes		>0.2	<0.01	>0.2

3. The defect in secretion is dependent or related to:

a. Control of diabetes: yes (7)
no (3)
b. Severity of diabetes: yes (6, 7)
no (3, 5)
c. Duration of diabetes: yes (4, 6)
no (3, 5, 7)

All investigators agree that no consistency can be observed in pattern of secretion.

One explanation of these reported differences is the question of comparability of data due to differences in secretory test techniques, interpretation of data, and patients studied.

This third factor is of considerable importance. At present, there are no certain means of determining in any single patient whether his diabetic state derives from classical diabetes mellitus, pancreatic islet deficient diabetes or both.

This can be alternately stated as whether there is α cell defect, β cell impairment or an imbalance between both. Moreover, there still exists an unresolved question as to whether there is a fundamental difference between juvenile diabetes and maturity onset diabetes.

TABLE VI

Mean Secretin Test Data of Patients (66) with Diabetes and Various Types of Cirrhosis

	#	Mean Volume ml/kg	Mean Max (HCO$_3$) mEq/L	Mean Amylase μ/kg
Hemachromatosis	38	9.2	102	32.7
Cirrhosis	17	3.8	84	18.2
Cirrhosis and Chronic Pancreatitis	11	4.1	100	23.2
Normal Range		2.0 – 4.0	90 – 137	

Overall perusal of the observed data indicates there are statistical significant decreases in the maximum bicarbonate concentrations, most markedly in the juvenile diabetics. There are significant increases in rates of flow. Minimal changes in rates of enzyme secretion, increased in adult onset diabetes, decreased in juvenile diabetes. These findings suggest that diabetic states are associated with at least minimal inflammation and fibrosis of the exocrine parenchyma.

The question as to whether pancreatic inflammatory or neoplastic disease may produce a diabetic state can be answered unequivocally yes. The simplistic explanation states that the exocrine disease destroys sufficient islet tissue to cause insulin deficiency. Yet there is poor correlation between the existence and severity of diabetes and the histopathology. Moreover, in pancreatic cancers, especially involving the tail, diabetes appears as an early prodromal symptom before significant parenchyma is involved. In addition, the age group of patients with pancreatic cancer, presents the possibility of unrelated onset of adult diabetes.

The clinical implications of the data would suggest that diabetic patients complaining of diarrhea and/or steatorrhea should be tested to exclude deficient pancreatic secretion. Such patients might benefit from oral pancreatic enzyme supplementation. Moreover, the diarrhea and steatorrhea observed in juvenile diabetes has often been related to so-called diabetic neuroenteropathy. These symptoms most probably derive from pancreatic insufficiency, the existence of which I (DAD) have previously observed in these patients. Finally, in patients with gall bladder disease, those with diabetes secreted, on the average, less bicarbonate than those without diabetes. The implication, again, would be that unresponsive diarrhea in patients with gall bladder should be studied for pancreatic secretory deficiency.

Conclusions

Diabetes is associated with a significant incidence of abnormal pancreatic exocrine deficiency. The pathogenesis of the alterations of secretion is unknown. The patterns of abnormal secretion observed in diabetics are varied and do not show good correlation with diabetic control, severity, or duration of disease. Diarrheas in diabetics should be investigated for deficiency of exocrine secretion and may benefit from replacement therapy. The diabetes in patients with pancreatic inflammation or cancers cannot be explained as simple islet destruction.

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Involuntary Movements Induced by Anticonvulsant Drugs

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Abstract

Various types of involuntary movements induced by anticonvulsant drugs have been recognized in recent years. Choreoathetosis, dystonia, orofacial dyskinesia, asterixis, myoclonus, ballismus, postural tremor, bradykinesia, and abnormal eye movements have all been reported. All these readily disappear following drug withdrawal or dose reduction and, in some cases, following administration of anticholinergic drugs. Two additional cases of phenytoin-induced movement disorder are presented. One patient exhibited choreoathetosis, dystonia, and ballismus, the other one exhibited asterixis.

Introduction

Involuntary movements (IM) are a well recognized complication of drugs that alter the interaction between neurotransmitters and receptors in the striatum. Neuroleptics, particularly the phenothiazines, are well known to produce such alteration inducing a variety of IM each of which is thought to be caused by hyper- or hypoactivity of certain type of neurotransmitter or receptor. The IM induced by anticonvulsant drugs have been frequently associated with phenytoin. This complication, however, still remains underrecognized to date despite previous case reports. We describe two cases of phenytoin induced IM to emphasize their frequency of occurrence.

Case Report

Case 1: A 21-year-old mentally retarded man had received various combinations of anticonvulsant drugs for a refractory mixed seizure disorder since childhood. Details of the past medical and family histories were not available except that the mother reportedly had vaginal bleeding during the first trimester of pregnancy. He was institutionalized following abandonment by his parents. The following laboratory tests were normal: hemogram and sedimentation rate, urinalysis including amino acid screening, biochemical screening, serum and urine osmolarity, thyroid function, skull and chest roentgenograms, and audiogram. An electroencephalogram (EEG) showed major, bilateral paroxysmal spike discharges, variable in location and occurring every 10–20 seconds throughout both the waking and sleeping portions of the tracing. A CT scan showed mild ventricular dilatation without demonstrable abnormalities in the white matter or corpus striatum.

On several occasions prior to initial evaluation, periods of lethargy, ataxia, and "wild tremors" developed following increment in the dosage of phenytoin and valproic acid. No other causes were found to account for these symptoms.

When first seen at age 20, the daily dosage (mg/day) of the following drugs were: phenytoin 500, carbamezapine 800, and valproic acid 1,500. Conspicuous during the examination was the presence of facial grimacing and continuous writhing, plus dystonic and flailing movements of the extremities and trunk, more prominent when under emotional stress. The tongue was in constant motion during attempted protrusion. Other significant findings were: somnolence, bilateral horizontal nystagmus, dysarthria, ataxia, gingival hypertrophy, and hirsutism. The remainder of the examination was unremarkable. The serum level of phenytoin was 25.7 μg/ml (therapeutic level 10-20) while the serum levels of carbamazepine and valproic acid were within the therapeutic range. The abnormal movements gradually disappeared within ten days following reduction of the dosage of phenytoin to 350 mg/

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day. As he became more alert, the dysarthria, ataxia and nystagmus became less profound, but the seizures became more frequent.

One month before hospital admission, ethotoin, 750 mg/day was added, and valproic acid discontinued later. The daily dosage of phenytoin (350 mg) and carbamazepine (800 mg) was maintained. One month after ethotoin was added, the abnormal movements recurred and this time they were more violent, requiring hospitalization. The serum levels of carbamazepine and ethotoin were within the therapeutic range while that of phenytoin was 21.2 μg/ml. The abnormal movements disappeared within three hours following administration of 1.0 mg intramuscular haloperidol. There were no new findings in the general physical examination. The hemogram and sedimentation rate, routine urinalysis, biochemical screening, and chest roentgenograms were normal. Ethotoin was discontinued totally on the day of admission but the daily dosages of phenytoin and carbamazepine were kept at 350 and 800 mg, respectively. The phenytoin level was kept below 20 μg/ml during the follow-up visits. The movement disorder has not recurred to date and the seizures remain poorly controlled.

Case 2: A 62-year-old woman sustained a cerebral concussion following a car accident six years prior to admission. Three years after the accident, she developed recurrent generalized tonic-clonic seizures requiring 300 mg of phenytoin daily with good control. She was noted to be forgetful and had lost the ability to calculate since the injury.

Two months prior to admission, she began complaining of dizzy spells and gait imbalance which were thought to be due to phenytoin toxicity. Despite reduction of the dosage of phenytoin to 200 mg daily, the symptoms continued to progress and, at the time of admission, she was incoherent, disoriented, and dysarthric.

The past history includes: endarterectomies for severe stenoses of the right innominate, carotid, and subclavian arteries nine years prior to admission; and ethanol abuse several years previously.

On admission, the abnormal findings included: somnolence, short attention span, memory loss, nystagmus in all directions of gaze, dysarthria, dysmetria, brisk deep tendon reflexes, and severe ataxia. The outstretched hands showed irregular flapping tremors that were more conspicuous with the wrists passively dorsiflexed. Irregular tremors of the tongue as well as irregular jerking at the shoulder and ankle joints were observed.

Except for slight normochromic, normocytic anemia and urinary tract infection, the remainder of the laboratory findings did not indicate any liver, renal or other metabolic disorders. An EEG showed irregular slow wave discharges more prominent on the right temporal area. The CT scan showed cortical atrophy that was more remarkable on the right temporal lobe. The serum level of phenytoin on admission was 43.0 μg/ml.

Phenytoin was temporarily withheld and over a period of four days marked improvement in her mental status and cerebellovestibular function was noted. The asterixis resolved completely in three days. The serum level of phenytoin ten days later was 6.8 μg/ml. She eventually admitted taking more than the required dose of phenytoin ever since her memory began to decline.

Discussion

Reports on various types of IM induced by anticonvulsant drugs are summarized in Table I (1–31). The IM (choreoathetosis, dystonia, and ballismus) exhibited by the first patient were clearly related to the toxic level of phenytoin. The associated signs consisting of somnolence, nystagmus, and ataxia; the disappearance of the abnormal movements following reduction of the dosage of phenytoin, and the absence of signs of infection or metabolic abnormalities, support this relationship. Since this patient is in a well supervised environment, it is unlikely that other drugs, like the phenothiazines, could be implicated as responsible for the abnormal movements. It is noteworthy that when the abnormal movements developed the second time, the phenytoin level was only slightly above the therapeutic range. It is conceivable that the ethotoin he was taking, a derivative of hydantoin, could have produced an additive effect to the already toxic level of phenytoin.

Since the choreoathetosis can be a presenting sign of systemic lupus erythematosus (32), and phenytoin has been reported to induce lupus-like syndrome (33), it is reasonable to suspect such occurrence in the first patient. Wilson's disease was also entertained. We did not specifically look for these possibilities because of the transient nature of the IM, lack of supportive clinical findings, and the benign clinical course of the patient.

The second patient exhibited signs of encephalopathy manifested by altered mental status, asterixis, and brisk reflexes in addition to nystagmus and ataxia. The improvement that followed reduction of phenytoin dosage and the absence of other metabolic abnormalities to explain the asterixis, suggested a causal relationship between the elevated phenytoin level and asterixis in this patient.

The induction of the IM in these two patients represent one of the many problems encountered in the management of epilepsy. Intractability of the seizures, as in the first patient, led to the use of several drug combinations at higher dosages. Unreliable drug intake, as in the second patient, are very common etiologic factors in anticonvulsant drug toxicity. Although the phenytoin-induced IM in all reported cases had been ameliorated promptly by drug withdrawal or dosage reduction, it may pose diagnostic difficulty to the unwary especially when cerebellovestibular signs are either mild or absent (9, 10, 14, 15, 20, 21).

It appears that regardless of the patient's age and sex, intellectual level, duration of therapy, drug combinations used, and status of seizure control, anticonvulsant drug-induced IM can potentially develop especially when the serum level is in the toxic range (Table I). However, one must be cognizant that it is often difficult to set a defined therapeutic or toxic range of serum anticonvulsant drug for each individual. Since IM have been observed to occur at presumably nontoxic range (18, 22, 24, 26, 28, 29, 31) or immediately following intravenous (IV) administration of phenytoin (3, 4, 28), a question of hypersensitivity or

TABLE I
Summary of Reports of IM Induced by Anticonvulsant Drugs

Author	Age/ Sex	Status of Seizure Control	Anticonvulsant Drugs Taken at Onset of IM	Offending Drug Duration of Treatment Serum Level	IM	Accompanying Signs of Toxicity (Mental and/or Cerebello Vestibular
Lazaro	21/M	Poor	Phenytoin Carbamazepine Valproic acid	Phenytoin 15 years Toxic	Choreoathetosis Dystonia Ballismus	(+)
	62/F	Good	Phenytoin	Phenytoin 3 years Toxic	Asterixis	(+)
Hajnsek & Sartorius (1964) 1	31/F	Poor	Carbamazepine Phenytoin	Carbamazepine 7 days Toxic	Postural tremor	(+)
Peters et al (1966) 2	29/F	Good	Phenytoin Phenobarbital	Phenytoin 11 years NS	Choreoathetosis Dystonia	(+)
Reimer et al (1967) 3	23/M	NS	Phenytoin	Phenytoin IM developed immediately following IV infusion NS	Ballismus Athetosis	(+)
	22/M	NS	Phenytoin	Phenytoin NS NS	Asynchronous rhythmic movements of the limbs	(+)
Diehl (1969) 4	54/F	Poor	Phenytoin	Phenytoin IM developed immediately following IV infusion NS	Dystonia Athetosis Hemiballismus	(+)
	26/F	Good	Phenytoin	Phenytoin IM developed immediately following IV infusion NS	Dystonia Athetosis	(+)
Logan et al (1969) 5	19/M	Good	Phenytoin Phenobarbital	Phenytoin NS Toxic	Choreoathetosis (Antedated phenytoin therapy)	(+)
Engel et al (1971) 6	48/M	NS	Phenytoin	Phenytoin NS NS	Asterixis	(+)

TABLE I—*Continued*
Summary of Reports of IM Induced by Anticonvulsant Drugs

Author	Age/ Sex	Status of Seizure Control	Anticonvulsant Drugs Taken at Onset of IM	Offending Drug Duration of Treatment Serum Level	IM	Accompanying Signs of Toxicity (Mental and/or Cerebello Vestibular
Prensky et al (1971) 7	9/M	Poor	Phenytoin Phenobarbital Paramethadione	Phenytoin 4 years Toxic	Bradykinesia Postural tremor	(+)
Gerber et al (1972) 8	34/F	Good	Phenytoin	Phenytoin 6 years	Choreoathetosis	(+)
Bellman & Haas (1974) 9	11/F	Good	Phenytoin Primidone	Phenytoin 11 years Toxic	Choreoathetosis	(+)
Kooiker & Sumi (1974) 10	40/F	Good	Phenytoin Phenobarbital	Phenytoin 3 years Toxic	Choreoathetosis Dystonia Flapping movements of upper extremities	(+)
	50/F	Good	Phenytoin Phenobarbital	Phenytoin NS Toxic	Choreoathetosis Dystonia Flapping movements of upper extremities	(+)
McLellan & Swash (1974) 11	31/M	Poor	Phenytoin Primidone Carbamazepine	Phenytoin 10 years Toxic	Chorea Asterixis	(+)
	15/M	Poor	Phenytoin Phenobarbital Primidone	Phenytoin 13 years Toxic	Choreoathetosis Dystonia	(+)
Murphy & Goldstein (1974) 12	60/M	NS	Phenytoin	Phenytoin 1 year Toxic	Asterixis Multiple myoclonus	(+)
	46/F	NS	Phenytoin Phenobarbital	Phenytoin NS Toxic	Asterixis Multiple myoclonus Static tremor	(+)
Rosenblum et al (1974) 13	9/M	Poor	Phenytoin Phenobarbital Ethosuximide	Phenytoin NS NS	Choreoathetosis	(+)
Shuttleworth et al (1974) 14	18/M	Poor	Phenytoin Phenobarbital	Phenytoin 18 years Toxic	Choreoathetosis	(−)
	39/F	NS	Phenytoin Diazepam	Phenytoin 16 years Toxic	Choreoathetosis	(+)
	37/M	NS	Phenytoin Phenobarbital	Phenytoin 27 years Toxic	Choreoathetosis	(+)
Ahmad et al (1975) 15	19/M	Poor	Phenytoin Sulthiame Phenobarbital Beclamide	Phenytoin 12 years Toxic	Choreoathetosis	(+)
	34/F	Poor	Phenytoin Phenobarbital	Phenytoin 10 years Toxic	Choreoathetosis	(+)
	28/F	Poor	Phenytoin Pheneturide	Phenytoin 10 years Toxic	Choreoathetosis	(−)

TABLE I—*Continued*

Summary of Reports of IM Induced by Anticonvulsant Drugs

Author	Age/ Sex	Status of Seizure Control	Anticonvulsant Drugs Taken at Onset of IM	Offending Drug Duration of Treatment Serum Level	IM	Accompanying Signs of Toxicity (Mental and/or Cerebello Vestibular
	60/F	Poor	Phenytoin Sulthiame Phensuximide	Phenytoin NS Toxic	Choreoathetosis Coarse finger tremor, jerking of upper limbs	(+)
Kirschberg (1975) 16	15/F	Fair	Ethosuximide Phenobarbital Phenytoin	Ethosuximide NS (?) NS	Choreiform and flailing movements Orofacial dyskinesia	(+)
Chadwick et al (1976) 17	51/F	Poor	Phenobarbitone Phenytoin Primidone Diazepam	Phenobarbitone 24 years Toxic	Asterixis	(+)
	67/M	NS	Phenobarbitone Phenytoin	Phenobarbitone 6 months Toxic	Asterixis	(+)
	66/F	Good control of trigeminal neuralgia	Carbamazepine	Carbamazepine 2 years Toxic	Asterixis	(+)
	59/F	NS	Phenytoin	Phenytoin 1 year Toxic	Asterixis Orofacial dyskinesia	(+)
	72/M	Good	Phenytoin	Phenytoin 1 year Toxic	Asterixis Orofacial dyskinesia Dystonia	(+)
	18/M	Poor	Phenytoin Carbamazepine Primidone Diazepam	Phenytoin NS Toxic	Chorea Dystonia	(+)
Chalhub et al (1976) 18	8/M	Poor	Phenytoin Primidone Ethosuximide Acetazolamide	Phenytoin 8 years Non-toxic	Choreoathetosis Dystonia	(−)
	8/M	Poor	Phenytoin Primidone Carbamazepine Methsuximide	Phenytoin 8 years Non-toxic	Choreoathetosis	(+)
Zinmeister & Marks (1976) 19	3/M	NS	Phenytoin Mephobarbital Primidone	Phenytoin NS Toxic	Choreoathetosis	(+)
Luhdorf & Lund (1977) 20	24/F	Poor	Phenytoin Phenobarbital	Phenytoin 12 years Toxic	Choreoathetosis	(+)
	20/F	Poor	Phenytoin Phenobarbital	Phenytoin NS Toxic	Choreoathetosis	(+)
	20/F	Good	Phenytoin	Phenytoin 13 years NS	Choreoathetosis	(−)
Rasmussen & Kristensen (1977) 21	66/F	Poor	Phenytoin	Phenytoin 3 years Non-toxic	Choreoathetosis	(−)

TABLE I—*Continued*

Summary of Reports of IM Induced by Anticonvulsant Drugs

Author	Age/ Sex	Status of Seizure Control	Anticonvulsant Drugs Taken at Onset of IM	Offending Drug Duration of Treatment Serum Level	IM	Accompanying Signs of Toxicity (Mental and/or Cerebello Vestibular
DeVeaugh-Geiss (1978) 22	55/M	NS	Phenytoin	Phenytoin 3½ years Non-toxic	Aggravated preexisting tardive dyskinesia	(−)
Opida et al (1978) 23	28/M	NS	Phenytoin Phenobarbital	Phenytoin 18 days Toxic	Ballismus Asterixis	(+)
Berchou & Rodin (1979) 24	8/F	Good	Carbamazepine Phenobarbital Phenytoin	Carbamazepine 13 days Non-toxic	Oculogyric crisis	NS
Crosley & Swender (1979) 25	5/M	Good	Carbamazepine	Carbamazepine 10 days NS	Dystonia Opisthotonic posturing	(−)
	10 mon/ M	Poor	Carbamazepine Phenytoin	Carbamazepine 21 days NS	Dystonia Opisthotonic posturing Grimacing	(−)
	4/M	Poor	Carbamazepine Phenytoin Phenobarbital	Carbamazepine within 3 weeks NS	Dystonia Opisthotonic posturing Grimacing	(−)
Hyman et al (1979) 26	31/M	NS	Sodium Valproate Phenobarbital Primidone	Sod. Valproate 13 months Toxic	Postural Tremor	NS
	48/M	NS	Sodium Valproate Phenytoin Primidone	Sod. Valproate 14 months Non-toxic	Postural Tremor	NS
	26/F	NS	Sodium Valproate Phenobarbital	Sod. Valproate 14 months Non-toxic	Postural Tremor	NS
	52/M	NS	Sodium Valproate Carbamazepine	Sod. Valproate 3 months Non-toxic	Postural Tremor	NS
Jacome, D (Personal observation in 4 pts. (1979) 27	ND	ND	ND	Carbamazepine ND ND	Dystonia	ND
Mauguiere et al (1979) 28	16/M	Poor	Phenytoin Phenobarbital	Phenytoin IM developed within 24 hrs following IV infusion Non-toxic	Choreoathetosis	(−)
Nausieda et al (1979) 29	72/F	Good	Phenytoin Phenobarbital	Phenytoin 4 years Non-toxic	Choreoathetosis	(−)
	52/M	NS	Phenytoin	Phenytoin 2 days Non-toxic	Orofacial dyskinesia	(−)
Joyce & Gunderson (1980) 30	51/M	Poor	Carbamazepine	Carbamazepine	Orofacial dyskinesia	(+)

TABLE I—*Continued*
Summary of Reports of IM Induced by Anticonvulsant Drugs

Author	Age/ Sex	Status of Seizure Control	Anticonvulsant Drugs Taken at Onset of IM	Offending Drug Duration of Treatment Serum Level	IM	Accompanying Signs of Toxicity (Mental and/or Cerebello Vestibular)
Bodensteiner et al 31 (1981)	29/F	Poor	Sodium Valproate Phenytoin	Sod. Valproate 6 months Non-toxic	Asterixis	(−)
	27/M	Poor	Sodium Valproate Carbamazepine Primidone	Sod. Valproate 8 months Non-toxic	Asterixis	(+)

NS—Not specified.
ND—No details.
(+)—Present.
(−)—Absent.

idiosyncratic reaction may be raised. Similarly, IM have been observed within a short period following oral administration of ethosuximide (dyskinesia) (16) and carbamazepine (oculogyric crisis) (24).

The mechanism by which anticonvulsant drugs, especially phenytoin, act in the striatum and thereby induce or facilitate IM is still unknown. Review of the literature suggests that IM are more likely to occur in individuals with low intellect or with pre-existing brain lesions particularly in the striatum (14, 18, 20, 21, 25, 29). Such is the case with our first patient even though the striatum appeared unremarkable radiologically. The observation that IM in Huntington's chorea worsen with phenytoin (34) and partially alleviated with dopamine blocking agents, like phenothiazines and reserpine (35) would suggest that alteration in the sensitivity of the dopamine facilitated striatal neurons may underlie the mechanism by which anticonvulsant drugs, like phenytoin, induce IM. However, other IM like asterixis, postural tremor, myoclonus, and ballismus, may have a different and complex mechanism.

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Sympathetic Blockade as a Diagnostic and Therapeutic Technique

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Abstract

The part played by sympathetic nerve blocks in the treatment of chronic pain is discussed as well as diagnostic uses of sympathetic nerve blocks. Indications, techniques and complications are stressed.

Fortunately, most pain is transient. It either improves by itself, or it responds to rest, analgesics, antibiotics, antirheumatics, or appropriate surgical treatment.

When pain does not disappear, it becomes chronic. The patient becomes more anxious, fearing that there is no help for him, especially if his physician or other referred specialists are unable to permanently relieve this pain. Indeed, some have branded this patient a neurotic, a hypochondriac, or a compensation-seeker. Sometimes this is true. Most frequently, suffering continues, depression follows and the patient cannot function at work and at home. He becomes difficult to live with and withdraws into himself. Relationships with family and friends deteriorate. Many man-hours of work are lost to the country because of intractable pain.

No patient should undergo treatment for intractable pain without full investigation, and an etiologic and anatomic diagnosis. Assistance in diagnosis must be sought from all specialties involved in the particular pain process. A multidisciplinary approach to the patient's whole problem should be employed. He might require psychologic testing, psychotherapy, physical therapy, occupational therapy, drug detoxification and/or other forms of treatment.

Pain cannot be accurately measured. Generally, an algorithm scale (0–10, with ten as the maximum) is used as a subjective measurement.

Visceral pain differs from somatic pain in a number of ways. Somatic pain is sharp, localized and precise, whereas visceral pain tends to be vague, burning, nagging, poorly localized and often referred.

It is advantageous to block an autonomic nerve rather than a somatic nerve, (1) because somatic nerve block may cause motor paralysis, numbness and proprioceptive loss. On the other hand, with an autonomic block, the patient will continue to function normally with no pareses or sensory deficits. In the case of a cervical sympathetic block, only a Horner's syndrome and an absence of sweating in the area involved could occur, discomforts which can easily be tolerated by most patients.

In the past, it was thought that the autonomic nervous system did not possess pain fibres and did not contain sensory afferents, as bowel and blood-vessels could be cut, clamped, and cauterized without causing pain. However, we do know that obstruction of a hollow muscular system causes severe cramps, distension of bowel or stomach causes pain, and vascular spasm and frost-bite cause overwhelming burning pain. These sensations are carried by sympathetic afferents.

Sympathetic blockade can be achieved by various techniques, including spinal and epidural routes, but somatic nerves would also be blocked. By blocking sympathetic ganglia, a pure sympathetic blockade will result. The entire peripheral sympathetic nervous system can be reached at three sites.

The sympathetic trunk is a bilateral structure consisting of ganglionated nerves from the base of the skull to the coccyx. It receives preganglionic connections from T1 to L2. The ganglia lie on both sides of the vertebral column. In the neck, they are concentrated into the superior, middle and inferior (better known as the stellate) ganglia. In

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the abdomen, they are concentrated into the celiac and lumbar sympathetic ganglia. At these three points—stellate, celiac and lumbar sympathetic ganglia—the entire peripheral sympathetic nervous system can be reached (Fig. 1).

Prior to performing any of these blocks, certain steps must be taken:

1) Resuscitation equipment must be available and in good working condition.
2) There must be fully informed consent and the consent form signed.
3) Sterile technique must be employed.
4) A test dose must be administered before the therapeutic dose is given.
5) Aspiration must precede the injection to avoid intravascular injection.
6) No block should be performed when the patient is anticoagulated.
7) Bilateral blocks should not be performed, as complications are increased. A stellate block may paralyze the recurrent laryngeal nerve as well. If this occurred bilaterally, the airway would be compromised. Bilateral celiac and lumbar sympathetic blocks can cause severe hypotension.
8) It is important to remain in contact with the patient as the onset of syncope or coma may not be recognized.

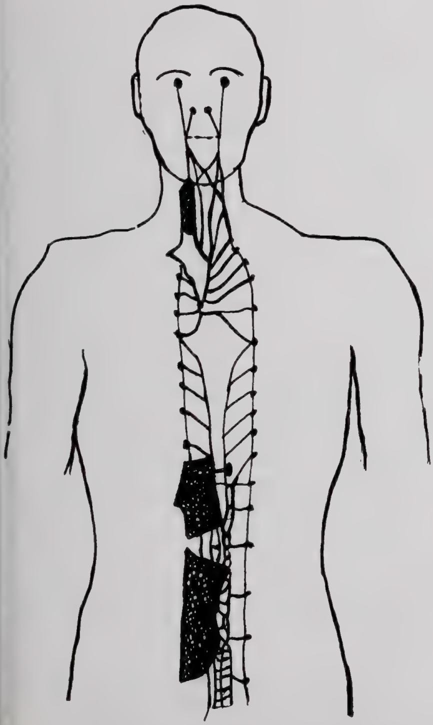

FIG. 1. Shows the accumulations of sympathetic fibers in he stellate, celiac and lumbar sympathetic ganglia.

Indications for Sympathetic Ganglionic Blocks

Phantom Limb Pain: True phantom limb pain is not common. Many so-called phantom limb pains are caused by the presence of stump neuromata or scar formation with nerve structures intertwined within. If its presence is suspected, and the affected stump is vasoconstricted and sweating, sympathetic blockade may be tried. Usually a few injections with local anesthetic into the necessary ganglia every five days will suffice.

Causalgia follows partial nerve interruptions, commonly the median, sciatic or tibial nerves. It usually follows a violent or rapid injury, such as from a missile or crush injury. The pain may start immediately or weeks or months later. Repetitive or prolonged stimuli may initiate bouts of pain. The degree of pain appears to be out of all proportion to the stimulus. It is an unpleasant burning sensation. Paraesthesiae and hyperesthesia occur, and these do not always follow the dermatomal distribution. These cases frequently respond to sympathetic nerve block with local anesthetic (2, 3) administered every three to five days for about five injections.

Reflex sympathetic dystrophy (4) remains a mysterious ailment. Trivial or minor injuries are responsible for this state. Frequently the symptoms appear to be psychogenic. If left untreated, this condition deteriorates into an irreversible situation and marked secondary, pathologic and psychologic changes occur.

First there is the stage of denervation. This may occur soon after injury or follow weeks or months later. There is an increase of blood flow to the extremity. The limb is warm, red and edematous; the skin is dry and there is an increase in nail and hair growth. The arm is held flexed and close to the body to minimize dependent perfusion. There is a burning pain and the skin is hyperesthetic to light touch.

The phase of hypersensitivity follows. Pain, hyperesthesia and paresthiae continue. Now there is an increase in sympathetic activity and a hypersensitivity to circulating catecholamines. Vasospasm occurs and the skin of the extremity becomes cool, grey, pale and cyanotic. Spongy edema makes way for brawny edema. Trophic changes now develop, glossy skin and diminished nail and hair growth. Ischemic pain may be present. It is aggravated by movement, emotion, noise, lights, and vibration. Behavioral changes are noticed. The patient becomes withdrawn, depressed and irritable. He covers his limb with towels and is terrified that he may be touched. His life centers around his extremity. He is often considered neurotic or paranoid.

The third stage is one of reinnervation. Symptoms persist, but a regeneration of sympathetic perivascular fibres commences and skin temperature, skin and nail growth return to normal. But there is disuse atrophy, muscular wasting, pericapsular fibrosis (stiff joints, claw hand and frozen shoulder). There are muscular contractures, Sudek's atrophy, and osteoporosis. The patient is left with the deformities. Those who called him neurotic are embarrassed when attempting to explain the deformities.

Hemiplegics and, occasionally, patients with angina may develop a reflex sympathetic dystrophy.

Surgical and medical treatment are of little value in this condition. Sympathetic blockade may dramatically improve the situation. After a few blocks with local anaesthetic, the pain begins to disappear, the leg will again bear weight, the towel is removed from the arm and vascular changes disappear. However, if sympathetic block is done too late in the course of the disease, deformities will remain.

Peripheral vascular disorders will frequently respond to a sympathetic block. In Raynaud's disease and peripheral vascular disease, relief of symptoms may occur from such a block, albeit temporary. Here it is utilized as a diagnostic tool, suggesting that if there is a response for a few hours then the patient should do well as a result of a cervical or lumbar sympathectomy. However, in a number of patients considered too ill to undergo surgery, lumbar sympathetic and stellate ganglion block, utilizing 6.8% phenol in water, have been performed with good results.

Arterial emboli can be rendered less destructive by an early sympathetic blockade until arrangements for embolectomy are completed. Lumbar sympathetic block may help to control ischemic ulceration of the legs.

The rare case of accidental injection of sodium pentothal or other drugs intra-arterially should immediately be followed by a stellate ganglion block to prevent or minimize damage. Similarly, if a radial artery cannulation results in thrombosis, embolisation or spasm, stellate block should be performed as soon as possible.

Postherpetic neuralgia is a painful and intractable condition frequently requiring a nerve block. Intercostal blocks have proved to be valueless in this situation as the lesion is proximal to the block. However, if administered early in the course of the disease, the pain of herpes zoster anywhere on the body, can be stopped or lessened by the appropriate sympathetic ganglion block, repeated on a few occasions.

Aneurysm of the aorta may cause severe backache due to pressure on nerves and bone. Stellate block has been of value in relieving this pain.

Angina pectoris, too, could be relieved by a similar block, but no one would suggest that it be utilized, and so negate an important danger signal.

In the past, cerebrovascular accidents have been treated with stellate ganglion blockade, with varying opinions as to the results. However, this mode of treatment has been abandoned.

Orthopedic cause of pain, such as chronic backache, the severe pain of Paget's disease of bone, chronic pains in the legs, have all at times responded to blockade of the lumbar sympathetic ganglia.

Hypertension following coronary artery bypass graft, has been a difficult problem to handle in the intensive care unit. Of late, stellate ganglion block has been described to be of value in this condition (5, 6).

Metastatic carcinoma involving the axilla, arising originally from the breast, pain in the arm following radiotherapy to the axilla, malignant tumors of the head and neck and pain due to bladder, uterine and prostatic carcinoma may all show varying degrees of improvement as far as the pain is concerned, when the appropriate sympathetic ganglia are blocked on a few occasions with local anaesthetic solution. Here, phenol could be used, if deemed necessary, for long term relief.

Prolongation of the QT interval. There is a condition of prolongation of the QT interval, unrelated to electrolyte disturbance or any medications, which is a heredofamilial condition. This is described as the Romano-Ward syndrome (7), or, when accompanied by deaf mutism, the Jervell-Lange-Nielsen (8) syndrome. These patients have perfectly normal hearts, except that the QT interval is longer than 0.4 seconds. There may be a history of syncope, or a family history of syncope or sudden death. Occasionally a U wave is present and sometimes alternating upright and inverted T waves.

These individuals are prone to sudden death. They may lead normal lives until moments of stress or emotional involvement, when there is an outpouring of catecholamines. Cardiac rhythm

TABLE I

Record for Sympathetic Blocks in the Past Two Years

Sympathetic Blocks	Disease	*Satisfactory Results* (Therapeutic or Diagnostic)	Complications
Stellate Ganglion Block 65	20 Sympathetic Dystrophy	14	Horner's Syndrome and hoarseness in almost all cases. Occasionally, difficulty in swallowing. There were no cases of pneumothorax.
	12 Vascular	8	
	2 Prolonted QT Syndrome	2	
	4 Leiomyoma Shoulder	4	
	1 Post-Herpetic Neuralgia	0	
	15 Chronic Pain in Arm	10	
	4 Chronic Pain in Face	2	
	4 Chronic Pain Upper Chest	0	
	2 Scapulo Humeral Syndrome	0	
Celiac Plexus Block 80	49 Carcinoma of Pancreas	40	1 Hypoalgesia and paraesthesiae in groin. 15 postural hypotension—2 developed ST depression (cleared up with hydration and electrolyte restoration). 1 cerebrovascular accident. 2 died—no autopsy—unknown if related to block.
	25 Chronic Pancreatis	18	
	4 Crohn's Disease	0	
	1 Retroperitoneal Metastasis	0	
	2 Multiple Laparotomies	0	
Lumbar Sympathetic Block 50	10 Sympathetic Dystrophies	10	Backache for a few days occurred in both the celiac and lumbar sympathetic blocks. Otherwise, no other complications noted.
	22 Vascular	14	
	2 Postlaminectomy Back Pain	0	
	4 Pelvic Pain	4	
	6 Chronic Pain Lower Limbs	2	
	4 Chronic Low Back Pain	0	
	2 Postparaplegic Leg Pain	2	

may then be altered by premature ventricular contractions, ventricular tachycardia, and, if the R falls on T, ventricular fibrillation (7).

Such is the fate of these patients that most ended life prematurely and suddenly. Digitalis, quinidine, dilantin and lignocaine have no effect on this condition. Only propranolol had had some success in prolonging life in these individuals provided they remain on this drug for the rest of their lives.

But a left stellate block will always stop the dysrhythmia during such an episode (9, 10). The block must be left-sided as the left stellate ganglion is responsible for the inotropic action of the heart and the right one for the chronotropic action (11). Following the block, the QT interval shortens and regular sinus rhythm returns. Once a good response is seen, it would be advisable to refer this patient for cervical sympathectomy, remembering that prior to surgery, the patient should be given a stellate block to prevent the effects of an endogenous catecholamine release which may occur on induction of anaesthesia.

Carcinoma of the pancreas, chronic pancreatitis and retroperitoneal metastases

Pain caused by pancreatic carcinoma or metastatic spread to the retroperitoneal region may be very severe necessitating frequent use of narcotics in ever-increasing doses. At times, it is only the pain and the somnolent effect of the narcotic-analgesia that keeps the patient in bed. A celiac plexus block frequently relieves the pain and allows the patient to return to work and continue a productive life. A travel agent with carcinoma of the pancreas, who was bed-ridden, went back to work for two years following a celiac plexus block. She then died of metastases, but painlessly. A school teacher with chronic pancreatitis who was about to undergo surgery, was given a celiac plexus block. His pain was relieved and he returned to teaching. Numerous other examples can be cited. Absolute alcohol is employed in these blocks.

Complications of Stellate Ganglion Block

1) Recurrent laryngeal block. This occurs in most cases and the patient should be reassured that the hoarseness will soon recover. As has already been stated, bilateral stellate block may result in loss of the airway.
2) Pneumothorax is certainly a possibility, considering that the level of the block is at C7, while the dome of the pleura extends into the neck almost to C7. Some people prefer to block at the level of C6 and claim equal results.

3) Deep bleeding from vertebral vessels.
4) Intrathecal injections.
5) If large volumes of agent are injected, large areas will become involved. Many other nerves can become anaesthetised, such as the phrenic nerve, vagus and brachial plexus.

Complications of Celiac Plexus Block

1) Penetration into aorta or inferior vena cava. This is never a problem, provided that the needle is withdrawn and nothing is injected.
2) Hypotension. This is even more of a problem if both sides are done. Simultaneously hypotension may soon be compensated for by the reflex response of the body. Occasionally it is long lasting, necessitating the use of intravenous fluids. Postural hypotension must be treated with elastic stockings and a tight abdominal binder. In any event, a celiac block should not be performed in the presence of pre-existing shock, dehydration and electrolyte disturbance.
3) Nerve roots to L1 and other nerves may be bathed in the alcohol injected, if adequate care is not taken to prevent such a situation from occurring. When the last of the alcohol has been injected, a few ml of air should be added in order that the retreating needle should not leave a track and so possible affect L1, which would leave the patient with pain or numbness in the inguinal region. Also, large quantities of solution are liable to spread over large areas affecting more nerves and other structures.
4) Intrathecal penetration is a possibility if the needle points too superficially.
5) Intraperitoneal penetration must obviously be avoided.

Complications of Lumbar Sympathetic Block

1) Neuralgia involving L1 is a distinct possibility.
2) Motor and sensory loss can occur when L1, L2, L3 and L4 nerves are affected. Weakness of the hip can be found on testing these patients, but it seldom interferes with walking. Small areas of sensory loss usually clear up in six months if a neurolytic agent has been used.
3) Hypotension can also occur, but less frequently than when the celiac plexus is blocked. Unlike the celiac block patients, these people can be ambulatory in most cases following the block.
4) Impotence may occur if a bilateral neurolytic block is done at the level of L1.

Techniques

Stellate Ganglion Block

The patient lies on his back on a flat surface looking straight in front of him. Chassagnac's tubercle—the most prominent transverse process palpable anteriorly is felt. This is C6. (some people inject here). C7 is the classical injection site. Measure off C7 below C6. This should be about 1½ fingers breadth above and lateral to the sternoclavicular joint. A skin wheal having been made, the sternomastoid and carotid artery are retracted laterally. The needle is then inserted until the transverse process of C7 is encountered. The needle is then withdrawn ¼″ and injection made.

Celiac Plexus Block

The patient lies prone on an x-ray cassette (padded), so that the x-ray will include the twelfth rib and sacrum. The body is slightly flexed to eliminate the lumbr lordosis. L2 is identified and marked with a marking pencil by counting down from the spine of C7, the first prominent spine palpable in the neck. Check by counting upwards from the intercristal diameter (between L4 and L5) until T12 is found. The body of L1 lies in front of the spine of T12 and the celiac ganglion lies antero-laterally to the body of L1 vertebra, with the aorta and inferior vena cava interposed on the left and right sides respectively.

At the level of the last rib and four fingers from the spine, a wheal is made. A 6″ long needle is used and it should be an 18″ guage or thicker, as a narrow bore needle tends to bend in the large back muscles. The needle is aimed at the body of L1 (which is at the level of the spine of T12). About 1½″ from the skin the transverse process may be felt. Direct the needle either above or below the transverse process for about another 1½″ until the body of the vertebra is encountered. The needle is "walked along" the bone, until the vertebral body is bypassed. The tip of the needle should be anterolateral to the vertebral body and the aorta or vena cava. If it is behind the aorta, but within the sheath (as evidenced by pulsations) it is considered to be in a satisfactory position, as the solutin will get to the ganglion. A-P and lateral x-rays are now taken to confirm the correct placement of the needle. If x-rays show that the needle is incorrectly placed, it must be

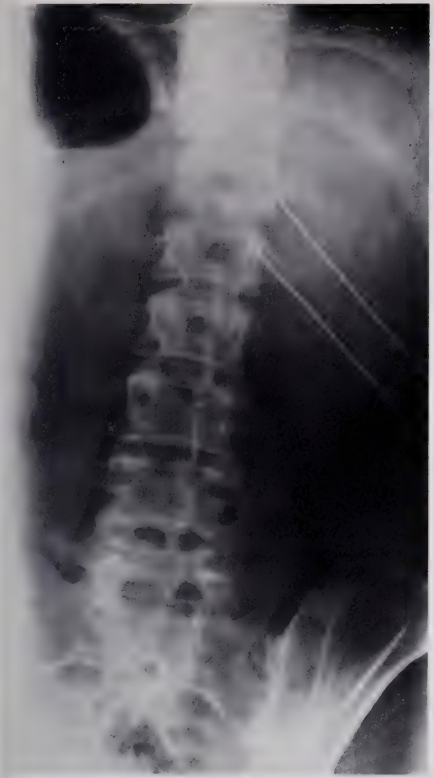

FIG. 2. A-P view of 2 needles for celiac plexus block. Upper needle considered too high, left in situ as a guide for lower needle (considered in good position).

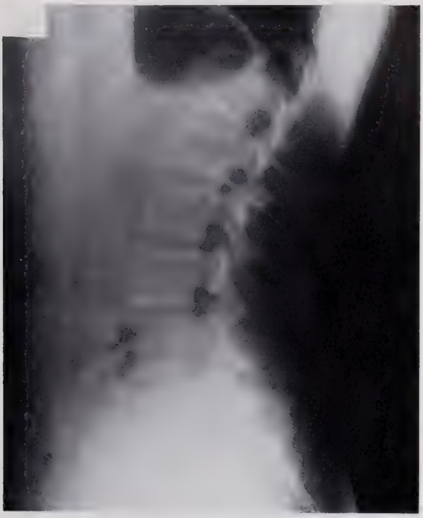

FIG. 3. Lateral view. Upper needle too high. Lower needle in good position for celiac plexus block.

repositioned and further x-rays taken until the position is satisfactory (Figs. 2, 3).

At this stage, 5 ml of 1% solution of xylocaine is injected. There should be pain relief and a slight fall in the systolic blood pressure. This is followed by a slow injection of 20 ml of absolute alcohol. After the first 5 ml or so have been introduced, the injection becomes painful and some demerol may have to be given. A few ml of air must be introduced, to prevent the formation of a track of leaking alcohol in the tissues. The patient should lie prone for about 45 minutes after the block.

Lumbar Sympathetic Block

The patient is positioned as for a celiac plexus block with an x-ray cassette under him. Vertebral

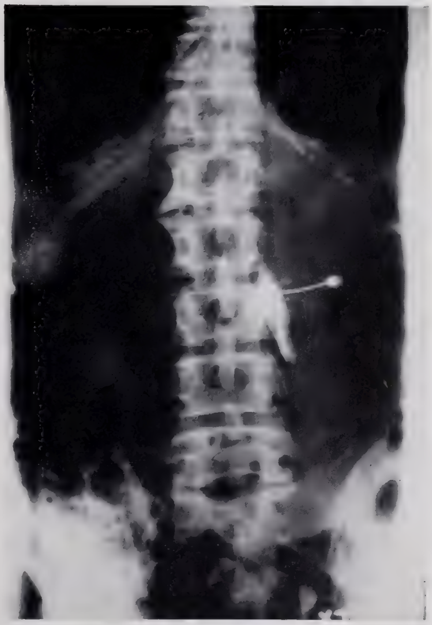

FIG. 4. A-P view of needle with contrast medium correctly placed at the level of L3 vertebra.

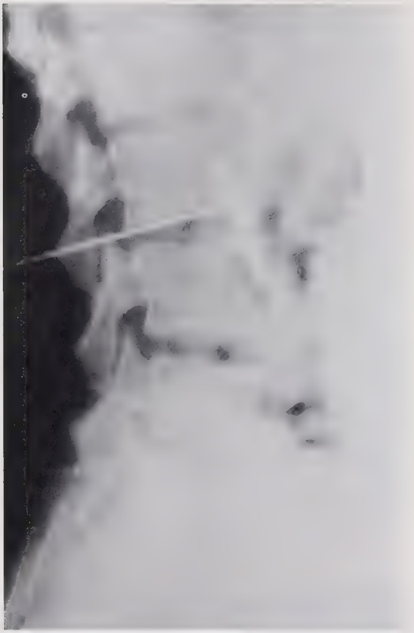

FIG. 5. Lateral view of needle correctly placed at level of L3 vertebra (with contrast medium).

spines L1 to L3 are marked. These are opposite the bodies of L2 to L4, generally. Through skin wheals three fingers from the mid-line, needles 6″ long and 18″ or 19″ gauge are placed adjacent to the required vertebrae. The needles for the celiac block, aiming for the arterolateral border of L2, 3 and 4, except that the tip of the needle should be more lateral than anterior. However, if a 5 ml glass syringe is attached to the needle on penetrating the psoas muscle, a resistance is felt not unlike that experienced while doing an epidural block. As soon as a loss of resistance occurs, the needle has passed through the psoas and its fascia and should be in the correct position. An injection of 1 ml contrast medium followed by A-P and lateral x-rays will show the placement of the needle, and also demonstrate the contrast medium—a linear streak lateral to the anterior surface of the vertebra suggests accurate placement of the needle, whereas a blob means that the tip of the needle is in the psoas (12, 13) (Figs. 4, 5).

One percent Xylocaine, absolute alcohol or 6.8% phenol in water is injected, depending on whether a diagnostic, therapeutic or permanent block is desired, the latter two being used only for permanent blocks (14).

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Genital Keratinocytic Dysplasia

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Abstract

Based upon personal experience with ten cases, this report reflects a distinct clinical and pathologic entity involving the genital skin and mucosa of young adults, all showing histologic features indistinguishable from squamous cell carcinoma in situ. This entity has been known for approximately 15 years and has masqueraded under a variety of terms which include bowenoid atypia of the vulva, vulvar atypia, multicentric pigmented Bowen's disease of the genitalia, multiple bowenoid papules of the penis, squamous cell carcinoma of the penis in young men and bowenoid papulosis. This entity encompasses a spectrum of different disorders which include bona fide in situ carcinoma (Bowen's disease), benign possibly viral-induced atypia and in situ carcinoma or benign atypia induced by viruses and/or podophyllin (long term effect) or other local irritative agents or factors on pre-existing lesions such as warts, seborrheic kerotoses or skin tags. Because all of the foregoing nomenclature is inappropriate, I recommend that this entity be termed genital keratinocytic dysplasia, biologic potential undetermined, and that the patient be treated conservatively.

During the past 15 years there have been reports in the medical literature of a distinct clinical and pathologic entity involving the genital skin and mucosa of young adults (1–11), all showing histologic features indistinguishable by light microscopy from intraepidermal or intraepithelial carcinoma (squamous cell carcinoma in situ). This report reflects my ideas about this entity gained from personal experience with ten such cases.

Observations

Table I represents a summary of the clinical data for each case. There were three women and seven men and the average age was 29, ranging from 21 to 36 years of age. Five cases had solitary lesions, but one of them (case 9) had had multiple lesions. The clinical sites involved were the penile shaft in four cases, the glans penis in one case, the vulva in two cases, the perineum in one case and the perianal skin in two cases. They ranged in size from 0.2 to 2.0 cm and showed variable colors which included skin-colored, white, tan, brown and erythematous. They were scaly or smooth-surfaced, appeared as papules, nodules and verrucous plaques and were soft or indurated. The duration of the lesions ranged from one month to three years. Six cases had received podophyllin therapy ranging from 11 days to six months before biopsy. The clinical diagnoses included warts, skin tags, seborrheic keratoses, papillomas, molluscum contagiosum and lichen planus. All lesions were asymptomatic and showed no evidence of spontaneous regression.

Histologically, all cases showed features indistinguishable from squamous cell carcinoma in situ. The epithelial cells involving virtually all epidermal or epithelial cell layers in portions of each lesion showed moderate to marked variations in size, shape, staining and polarity characteristics. Moderate to marked degrees of nuclear hyperchromatism and pleomorphism were present. Foci of dyskeratosis, nuclear and cytoplasmic vacuolar changes, necrotic keratinocytes, multinucleated giant cell forms and mitoses in prophase, metaphase and anaphase were identified in most cases. Although metaphase mitoses were prevalent and necrotic keratinocytes were more frequently encountered within the recently podophyllin-treated cases, these changes were also conspicuous within some of the nonpodophyllin-treated cases (Fig. 1), as well as with-

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TABLE I

Genital Keratinocytic Dysplasia

Case	Age	Sex	Site	Number	Appearance	* Size	Duration	** Podophyllin	Clinical Diag.	Other Relevant Data
1	32	F	Labia and clitoris	Hundreds	Tan, scaly indurated papules	0.3–1.0	One year	Six months	Verrucae	Symmetric involvement of labia majora, labia minora and clitoris; received multiple applications of 20% podophyllin in tincture of benzoin at 3 week intervals with no apparent clinical effect.
2	28	M	Perianal skin	Multiple	Skin-colored, scaly soft papules and nodules	1.0–1.5	Several months	Two weeks	Skin tags or condylomata acuminata	Internal and external hemorrhoids for several years; received 4 applications of 20% podophyllin in tincture of benzoin at 2 week intervals with no apparent clinical effect.
3	30	M	Shaft of penis	Several	Brown, scaly indurated papules, plaques and nodules	0.4–2.0	Several months	Eleven days	Seborrheic keratoses or verrucae vulgares	Received three applications of 20% podophyllin in tincture of benzoin at 2 week intervals with no apparent clinical effect.
4	28	F	Labia majora	Solitary	Skin-colored soft verrucous papule	1.0	A few months	*** __	Papilloma	None.
5	28	M	Shaft of penis	Solitary	Flat-topped, erythematous scaly indurated papule	0.8	Eight months	Six months	Lichen planus	Received several applications of 25% podophyllin in tincture of benzoin at 2 week intervals with no apparent clinical effect.
6	26	F	Perineum	Multiple	Skin-colored, smooth-surfaced and scaly soft papules	0.2–0.5	A few months	—	Condylomata acuminata	Simple vulvectomy 4 years ago for carcinoma in situ of both labia (biopsy diagnosis twice); electrosurgery, cryosurgery and podophyllin therapy proved ineffectual.
7	25	M	Glans penis	Solitary	White, scaly hard papule	1.0	One month	—	Molluscum contagiosum	None
8	34	M	Shaft of penis	Numerous	Tan, shiny smooth-surfaced papules	0.4–0.8	Four months	—	Verrucae planae	None
9	36	M	Shaft of penis	Solitary	Skin-colored verrucous plaque	2.0	Three years	Two weeks	Condyloma acuminatum	Had multiple lesions of penile shaft for 3 years; received several applications of 25% podophyllin in tincture of benzoin at 2 week intervals with regression of all lesions except one.
10	21	M	Perianal skin	Solitary	Skin-colored verrucous papule	0.5	Several months	Two weeks	Papilloma or verruca vulgaris	Received 3 applications of 20% podophyllin in tincture of benzoin at 2 week intervals with no apparent clinical effect.

* Size in centimeters.

** Time lapse between last local treatment and biopsy.

*** __ = No podophyllin therapy.

in cases last treated with podophyllin six months before biopsy (Fig. 2). In some cases, these changes appeared to be superimposed on a preexisting lesion such as a seborrheic keratosis (Fig. 3), an anal skin tag (Fig. 4) and a wart (Fig. 5). A polymorphous inflammatory cell infiltrate was invariably present within the subjacent cutis or lamina propria ranging from mild to severe, tended to be perivascular and was composed primarily of lymphocytes, histiocytes and neutrophils with plasma cells and melanophages in some cases.

Discussion

My findings raise some interesting questions. Can podophyllin produce pseudomalignant changes in other lesions such as seborrheic keratoses and skin tags besides condylomata acuminata? Can podophyllin exert long term effects and possibly induce malignancy? Do some of these cases fall into the category of so-called bowenoid papulosis of the genitalia? A brief review of what is known about podophyllin and the last named entity might help us to answer these questions.

Podophyllin is the dried resin from the roots and rhizomes of *Podophyllum peltatum* (may apple or mandrake). Podophyllotoxin, the active component, is a potent cytotoxin that arrests mitosis in metaphase, its action being qualitatively indistinguishable from colchicine (12). Topically, it is therapeutically effective in condylomata acuminata. Histologically, it may produce changes indistinguishable from intraepidermal carcinoma (squamous cell carcinoma in situ). It has been stated that these changes do not last longer than six weeks after therapy (13). My ob-

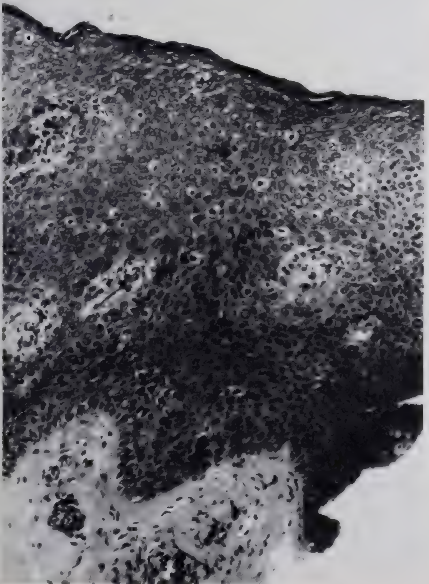

FIG. 1A. Low magnification of case 4 showing full thickness keratinocytic dysplasia with numerous metaphase mitoses (H & E ×100).

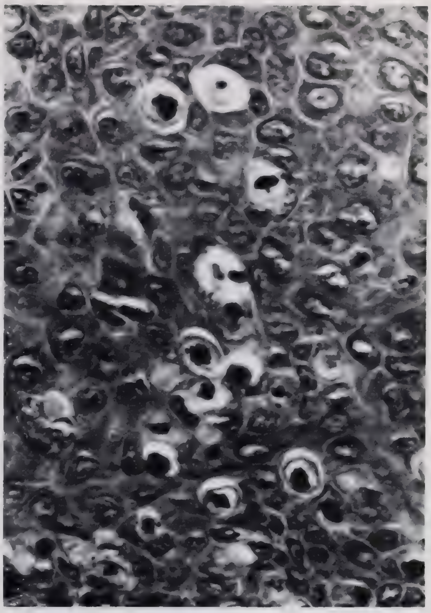

FIG. 1B. High magnification of Fig. 1A detailing metaphase mitoses and necrotic keratinocytes (H & E ×400).

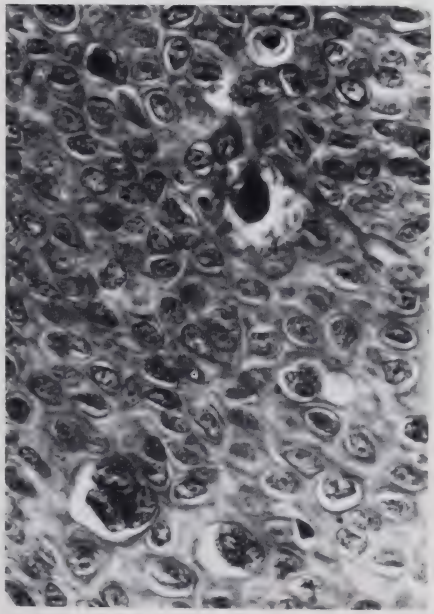

FIG. 1C. High magnification of Fig. 1A depicting multinucleated giant cells at bottom (H & E ×400).

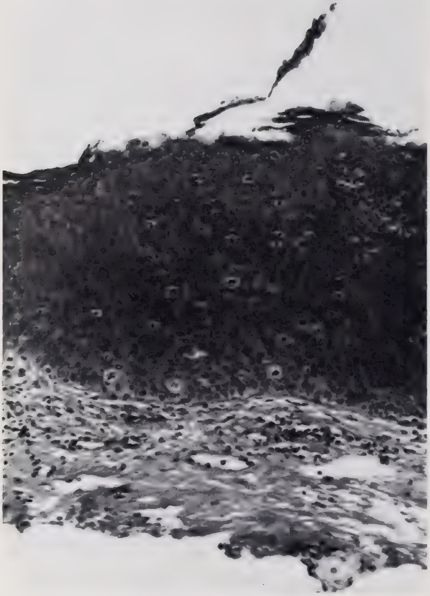

FIG. 2A. Low magnification of Case 1 showing full thickness keratinocytic dysplasia with numerous metaphase mitoses (H & E ×100).

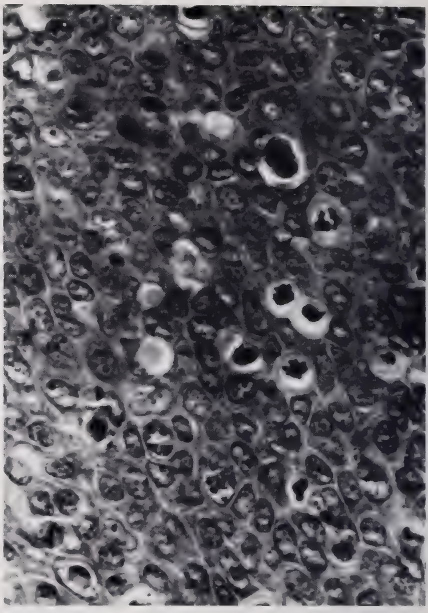

FIG. 2B. High magnification of Fig. 2A detailing metaphase mitoses and necrotic keratinocytes (H & E ×400).

servations in cases 1 and 5 either would seem to contradict this statement or would suggest that podophyllin might have the capacity to induce malignancy. Perhaps multiplicity of applications may be required for this change to occur on a long term basis.

As mentioned, so-called bowenoid papulosis of the genitalia is a distinct clinicopathologic entity which has been in the medical literature for about 15 years and has masqueraded under a variety of other terms which include bowenoid atypia of the vulva, vulvar atypia, multicentric pigmented Bowen's disease of the genitalia, multiple bowenoid papules of the penis and squamous cell carcinoma of the penis in young men.

Most of these lesions previously reported were multiple, but some were solitary. They tended to be slightly elevated, reddish, brown or violaceous indurated papules, either smooth-surfaced or with a slight scale, but verrucous plaques and nodules also occurred. They generally were asymptomatic, but some were mildly pruritic. The majority of cases had their lesions for several years prior to biopsy. In most cases the lesions regressed spontaneously within several months, but in some cases the lesions either persisted or new ones would develop while others regressed. A history of prior podophyllin therapy was elicited in several patients ranging from approximately two months to two years prior to biopsy. Several cases developed during or shortly after pregnancy. Genital herpetic infections had been present in some cases and viral particles have been demonstrated ultrastructurally in a few cases. By light microscopy all cases showed histologic features indistinguishable from intraepidermal or intraepithelial carcinoma. Response was generally excellent with virtually any therapeutic modality which included topical steroids, 5-fluorouracil and salicylic acid in collodion as well as surgical excision. No evidence of invasion or metastases has been reported.

Within the confines of this broad clinicopathologic spectrum, my experience leads me to believe that one might be dealing with several different disorders (Table II) which include bona fide in

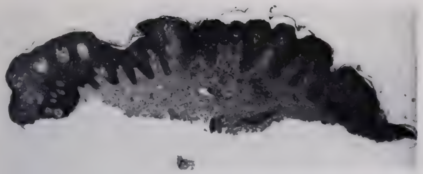

FIG. 3A. Scanning view of case 3 showing papillomatous pattern of a seborrheic keratosis (H & E ×20).

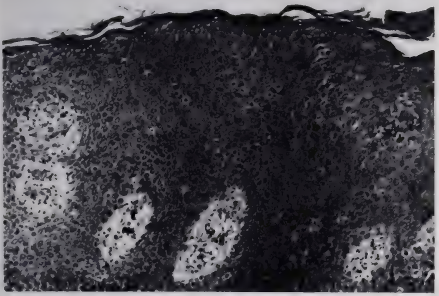

FIG. 3B. Low magnification of a portion of Fig. 3A showing prominent basaloid cell component and numerous metaphase mitoses (H & E ×100).

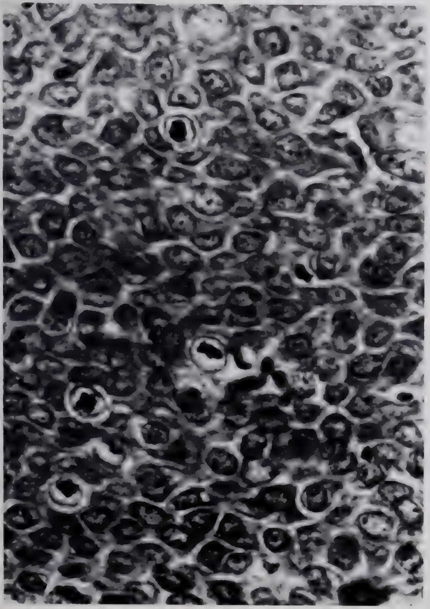

FIG. 3C. High magnification of Fig. 3B detailing features described (H & E ×400).

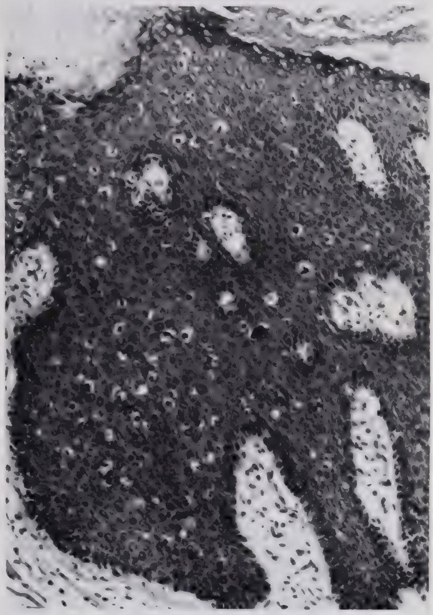

FIG. 3D. Low magnification of a portion of Fig. 3A showing full thickness keratinocytic dysplasia with numerous metaphase mitoses (H & E ×100).

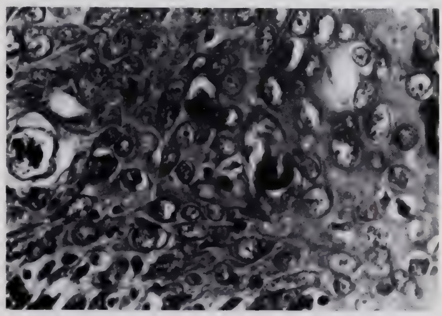

FIG. 3E. High magnification of Fig. 3D demonstrating keratinocytic dysplasia and necrosis along with exocytosis of inflammatory cells (H & E ×400).

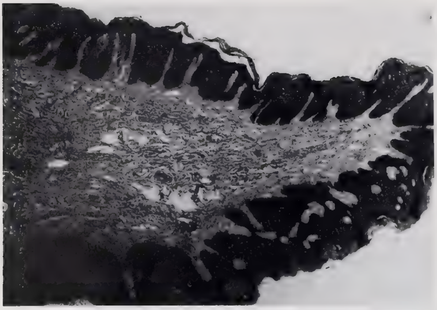

FIG. 4A. Scanning view of case 2 showing polypoid configuration of an anal skin tag with vascular connective tissue core (H & E ×20).

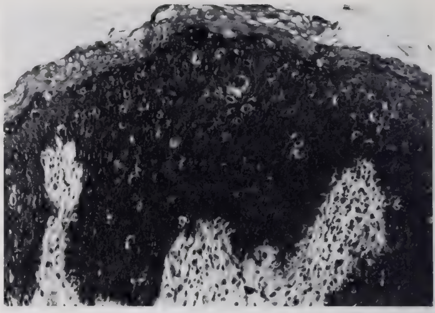

FIG. 4B. Low magnification of a portion of Fig. 4A demonstrating full thickness keratinocytic dysplasia and necrosis with numerous metaphase mitoses (H & E ×100).

situ carcinoma (Bowen's disease), benign possibly viral-induced atypia and in situ carcinoma or benign atypia induced by viruses and/or podophyllin (long term effect) or other local irritative agents or factors on pre-existing lesions such as warts, seborrheic keratoses or skin tags. In other words, one seems to be dealing with either true malignancies or pseudomalignancies.

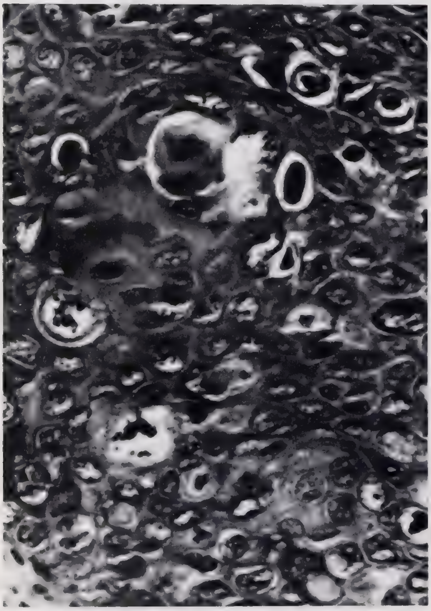

FIG 4C. High magnification of Fig. 4B detailing features described and also prophase mitoses (H & E ×400).

Thus, since the term bowenoid is ambiguous and confusing, since these lesions may not represent squamous cell carcinoma in situ or Bowen's disease, since they may present as a solitary lesion, since the genitalia of both sexes may be involved and since not all of them are papules, I believe that all of the foregoing nomenclature utilized for this entity is inappropriate. I therefore recommend that, given a patient with a lesion that falls within this clinicopathologic spectrum, the lesion be diagnosed genital keratinocytic dysplasia, biologic potential undetermined, and that the patient be treated conservatively with frequent follow-up visits.

Summary

Ten cases of a distinct clinicopathologic entity involving the genitalia of young adults have been analyzed. All cases showed histologic features indistinguishable from intraepidermal or intraepithelial carcinoma (squamous cell carcinoma in situ). One might be dealing with a spectrum of several different disorders which include bona fide in situ carcinoma (Bowen's disease), benign possible viral-induced atypia and in situ carcinoma or benign atypia induced by viruses and/or podophyllin (long term effect) or other local irritative agents or factors on pre-existing lesions such as warts, seborrheic keratoses or skin tags. In other words, one seems to be dealing with either true malignancies or pseudomalignancies. Because all of the foregoing nomenclature is inappropriate, I recommend that this entity be termed genital keratinocytic dysplasia, biologic potential undetermined, and that the patient be treated conservatively.

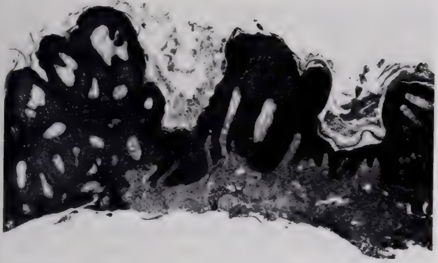

FIG. 5A. Scanning view of case 19 showing verrucous configuration (H & E ×20).

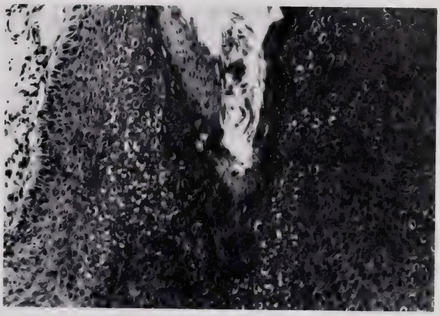

FIG. 5B. Low magnification of a portion of Fig. 5A showing vacuolar cytoplasmic changes and enlarged irregular hyperchromatic nuclei within malpighian layer characteristic of a condyloma acuminatum (H & E ×100).

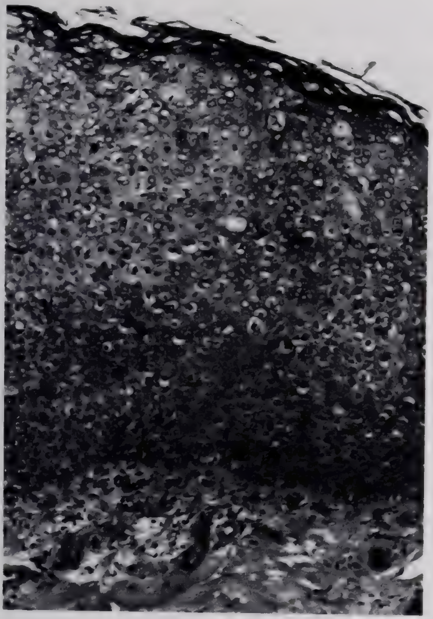

FIG. 5C. Low magnification of a portion of Fig. 5A showing full thickness keratinocytic dysplasia with numerous metaphase mitoses and prominent vacuolar changes (H & E ×100).

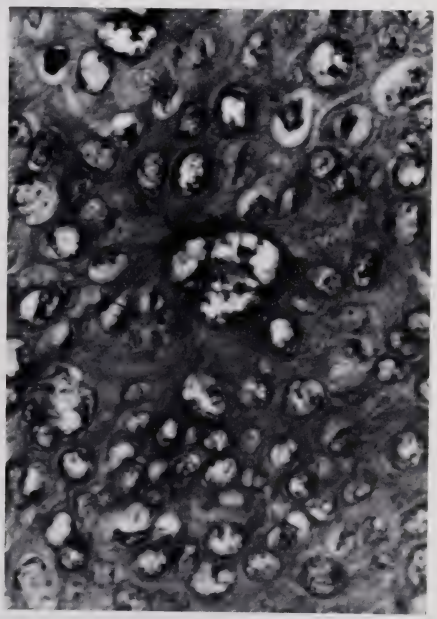

FIG. 5D. High magnification of Fig. 5C detailing features described and also a multinucleated giant cell (H & E ×400).

TABLE II
Genital Keratinocytic Dysplasia

Bona fide in situ carcinoma
Benign atypia (viral-induced?)
Secondary in situ carcinoma or benign atypia (viral-induced, long term podophyllin effect, other local irritative agents or factors, or any combination of the aforementioned) on preexisting warts, seborrheic keratoses or skin tags.

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Gonadotropin Producing Pituitary Adenomas. A Case Report and Review of the Literature

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Abstract

Production of FSH and LH is probably the least common endocrine function of pituitary adenomas. We report a 58-year old male with a pituitary adenoma, elevated FSH and LH levels, normal testosterone levels, and normal secondary sexual characteristics. Sixteen other patients with pituitary tumors and elevated gonadotropins have been described: five had high urinary gonadotropins by bioassay, six had high plasma FSH levels, two had high plasma LH levels and three had high plasma levels of both FSH and LH. Most patients were middle aged males. None had chromosomal abnormalities. The pituitary adenomas tended to be large and visual field involvement and hypopituitarism were frequent. Patients with high FSH and normal LH levels had low testosterone, variable degrees of eunuchoidism and hypospermatogenesis. Patients with high levels of both FSH and LH had normal testosterone levels and were eugonadal. Evidence in the literature suggests that patients with longstanding primary hypogonadism may have pituitary hyperplasia and/or pituitary microadenomas. To date, there is no evidence that these changes are the forerunner of the gonadotropin producing pituitary adenomas.

Introduction

Following the introduction of the radioimmunoassay, it became clear that most pituitary adenomas have endocrine function (1). Prolactin and growth hormone producing tumors are most common (2–4) and appear to arise spontaneously. Production of the other pituitary hormones is less frequent. ACTH producing adenomas are believed to be the likely cause of Cushing's disease (5) and are reported with increasing frequency (2–4). After adrenalectomy, these tumors may enlarge and give rise to Nelson's syndrome (6). Enlargement of the sella has also been described in a few patients with Addison's disease (7). TSH producing pituitary adenomas are rare and have similarly been reported to occur both as a cause of hyperthyroidism (8) and in longstanding primary hypothyroidism (9) presumably as a secondary phenomenon. Production of FSH and LH by pituitary adenomas appears to be least common.

In reviewing the literature, we found reports of sixteen cases (10–23) and no review of the subject. We report here a man with a pituitary adenoma and high FSH and LH levels. We also summarize the features of the previously reported sixteen patients with gonadotropin producing adenomas. Special attention is given to their gonadal function and to the possible relation that these tumors may have with preexisting primary hypogonadism.

Case Report

L. W. had normal sexual development, and had fathered one child at age 30. His sexual function had remained normal until he was 59 when he became gradually impotent. For many years, the patient consumed one pint of whiskey a day. The family history was negative. He was found to have an enlarged sella turcica at the age of 36. At 40, the patient developed headaches. At this time the visual fields, the urinary 17-hydroxysteroids and the thyroidal radioiodine uptake

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were normal and a pneumoencephalogram showed an intrasellar mass. He was treated with radiotherapy (4000 Rads) to the pituitary.

During the ensuing 16 years, the x-rays of the sella turcica did not change and the pituitary function remained intact except that reduced cortisol production was observed after 1966 when treatment with topical steroids was started for generalized neurodermatitis. The urinary gonadotropins (bioassay) were in excess of 26 MUU/day (normal 5-26) on two occasions.

On reevaluation at age 58, the patient appeared wasted, tremulous and chronically ill. His BP was 90/60, Pulse 102. The skeletal proportions were normal. The skin showed diffuse neurodermatitis. The pubic and facial hair were normal. There was no gynecomastia. The liver was enlarged (total span 18 cm). The penis and the prostate were normal. The testes measured 2.5 cm in length and were soft. Laboratory findings included: BUN 4, total protein 7.9, albumin 2.9, LDH 539, SGOT 254, hemoglobin 9.9. The liver function tests became normal during the first two weeks of hospitalization. The result of the endocrine function tests are shown in Table I. The testosterone levels were in the normal adult range but were clearly higher than predicted from the patients alcohol consumption, liver disease and old age. One of the FSH levels was in the normal range. All other FSH and LH titers were elevated. The sella turcica was 19 mm long and 13 mm deep. There was localized destruction of the floor and erosion of the posterior clinoids. Computerized axial tomography demonstrated an intrasellar mass. The visual fields were normal. The buccal smear was chromatin negative. The karyotype on peripheral leukocytes was 46XY. Testicular biopsy showed peritubular fibrosis and hyalinization, spermatogenic arrest and slightly hyperplastic Leydig cells.

TABLE I

Endocrine Function Tests

	Patient		Normal	
Test	Basal	Peak	Basal	Peak
Urinary gonadotropins (bioassay; n = 2)	50–100 (MUU/24h)**		0–25	
Urinary cortisol	20 μg/24h		30–120	
GnRH stimulation:				
Plasma FSH	25 (mIU/ml)	34	5–25	2–10 above basal value
Plasma LH	50 (mIU/ml)	106	16–30	20–110 above basal value
Ethinyl estradiol (0.5 mg tid for 3 days) suppression:				
Plasma FSH	27 (mIU/ml)	11	5–25	<50% decrease
Plasma LH	41 (mIU/ml)	17	16–30	<46% decrease
Plasma testosterone	689 (ng/dl)	122	300–1200	<70% decrease
Insulin hypoglycemia				
Plasma GH	<1 (ng/ml)	8	<5	>10
Plasma cortisol	3 (μg/dl)	5	5–25	>two-fold increase
TRH stimulation:				
Plasma TSH	1.5 (μU/ml)	5	6	8–40
Metyrapone Stimulation:				
Plasma 11-deoxycortisol	—	<0.1 (μg/dl)	—	>8
L-Dopa stimulation:				
Plasma GH	2 (ng/dl)	21	<5	>10
Plasma thyroxine	9.6 (μg/dl)		5–12	
Plasma triiodothyronine	154 ng/dl)		50–200	
Plasma prolactin (n = 4)*	11 ± 2 (ng/ml)		5–18	
Plasma FSH (n = 10)	31 ± 2.5 (mIU/ml)		5–25	
Plasma LH (n = 10)	58 ± 8.5 (mIU/ml)		6–30	
Plasma Testosterone (n = 10)	802 ± 38 (ng/dl)		300–1200	
Plasma Estradiol (n = 5)	6.7 ± 1.1 (ng/dl)		0.8–3.5	
Testosterone Binding capacity (n = 2)	1.7,20 (μg/dl)		0.9–1.9	
Urinary FSH (n = 6)	27 ± 1.2 (I.U/24h)		5–25	
Urinary LH (n = 6)	37 ± 2.3 (I.U/24h)		5–18	

* All assays were performed during a 3-month-period.

** Mouse uterine units.

Discussion

Selected clinical and laboratory features of the seventeen patients with pituitary adenomas and elevated gonadotropins are shown in Table II. Patients 1–5 had elevated urinary gonadotropins as measured by nonspecific bioassays. In the remaining twelve patients, plasma FSH and LH were measured separately by radioimmunoassays. Patients 6–11 had elevated FSH levels and normal LH levels. Patient 12 had elevated LH levels and normal FSH levels and patient 13 had high LH levels but her FSH was not measured. Patients 14, 15, 16 and our patient (17) had increased levels of both FSH and LH.

Thirteen of the seventeen cases were males and four were females. This prevalence of males may reflect underreporting of females. Since gonadotropins increase after the menopause, elderly women with pituitary adenomas and high gonadotropins are unlikely to be reported as examples of gonadotropin producing tumors. Ten of the males but only one of the females were over 45-years old. The sex chromatin and/or the karyotype were studied in seven patients and were normal. The measurements of the sella turcica were published in five cases and ranged from 17 to 35 mm in length (mean 23 mm) and from 11 to 20 mm in depth (mean 14 mm). One patient (n. 13) had a small pituitary adenoma which was demonstrated only at tomography.

Eight patients had visual field defects. Loss of vision was the presenting symptom in nearly one-half of the cases. Other common complaints were amenorrhea in females and impotence in males. The production of pituitary hormones other than FSH and LH was frequently abnormal. Eight of thirteen patients had decreased growth hormone, eight of seventeen had evidence of hypoadrenalism, and five of seventeen of hypothyroidism. Prolactin was elevated in five of eleven patients. Nine of the patients were explored surgically. All were found to have pituitary tumors which were classified as chromophobe adenomas. Seven of these tumors were studied in vitro.

In all seven, evidence of gonadotropin production by the tumor was obtained either by staining the tissue with specific anti-FSH and anti-LH antisera or by analyzing tissue cultures for hormonal products. Further evidence that the gonadotropin overproduction resided in the tumor was a fall in the gonadotropin levels of eight patients when the tumor was resected. The regulation of FSH and LH production was studied in nine patients. GnRH caused an exaggerated gonadotropin response in five patients and a normal or subnormal response in three. The administration of testosterone and/or estrogens suppressed gonadotropin levels in three of six patients but stimulated LH in one. A similar variability in regulation has been reported for the other types of pituitary adenomas (24). The gonadal function of patients with gonadotropin producing pituitary adenomas has varied. The three men with high urinary gonadotropins were eunuchoidal but no laboratory data exist to document the clinical findings.

Among the patients studied by specific radioimmunoassays a difference appears to exist between those with normal and those with elevated LH levels. Three of the six men with high FSH but normal LH levels were eunuchoidal, plasma testosterone was reduced in five, and spermatogenesis was defective in all four cases studied. In contrast the four men with high LH levels were clinically eugonadal and their testosterone levels were normal or elevated. The testicular biopsy in patients with high LH levels varied. It was normal in one and showed striking Leydig cell hyperplasia and tubular atrophy in another. The peritubular fibrosis and hyalinization found in our patient are nonspecific changes. They have been reported in various conditions including long term exposure to chorionic gonadotropin (25) and liver disease (26). While the elevated testosterone titers and the normal sexual characteristics of the patients with high LH levels may be expected, it is difficult to explain the low testosterone levels and the eunuchoidal features of the patients with high FSH but normal LH levels. Some of these patients may have had primary hypogonadism antedating the pituitary adenoma. As will be discussed later this appears to be improbable. A more likely possibility is that the overproduction of FSH by the tumor was secondary to abnormal regulation rather than being autonomous. For instance a reduction in LH levels, induced by the pituitary adenoma may have suppressed spermatogenesis and this may in turn have stimulated FSH production. A mechanism of this type is compatible with the recent report (27) that twelve of fifty men with pituitary adenomas had high FSH levels. It is also supported by the report of an acromegalic patient whose elevated FSH levels became normal when spermatogenesis was restored with GnRH (28). Further study is required however since other workers have found invariably low FSH levels in men with pituitary adenomas (29, 30).

Several of the authors of Table II (cases 1–6, 8, 13, 16) felt that gonadal failure in their patients had antedated the pituitary tumor and has possibly stimulated its development. Russfield et al

TABLE II

Pituitary Tumors Associated with Increased Gonadotropins

Patient #:	1	2	3	4
Author (Reference):	Lloyd (20)	Gordon & Moses (15)	Bower (10)	Kelly (16)
Age/Sex:	50/M	47/M	48/M	24/F
History: (Duration)	Impotence (many yr)	Impotence (5 yr) Cold intolerance (3 yr)	Lack of somatic & sexual development	Primary amenorrhea Lack of somatic & sexual development
Physical Findings:	"Hypogonadal"	Small testes, "eunuchoidal"	Small testes Gynecomastia Small penis	Absent sexual characteristics, short stature
Gonadotropins:				
Plasma FSH (or Urinary "FSH")	Urinary "FSH" 64 MUU/24h (5–25)*	Urinary "FSH" Pos. at 1:512	Urinary "FSH" >100 MUU/24h	Urinary "FSH" 40–100 MUU/24h
Plasma LH				
Plasma Testosterone				
Testosterone Suppression			No response	
GnRH Stimulation				
Sperm Count; Gonadal Histology	Tubular & Leydig cell atrophy			
Other pituitary functions:				
GH				
PRL				
TSH	Reduced	Reduced	Normal	? Normal
ACTH	Reduced	Reduced	Normal	
Sex Karyotype:			Chromatin Neg	Chromatin Pos
Sella Turcica (Size) & Tumor Morphology		35 × 20 mm	17 × 11 mm Chromophobe adenoma	20 × 12 mm
Tumor Function:				
Miscellaneous			Normal "FSH", Suppression after Estrogen	Normal "FSH" Suppression after Estrogen

Patient #:	5	6	7
Author (Reference)	Leiba et al (19)	Woolf & Schenk (23)	Friend et al (14)
Age/Sex:	36/F	28/M	60/M
History: (Duration)	Secondary amenorrhea (13 yr)	Loss of vision (2 yr) Infertility	Headache (10 yrs) Impotence (2 yr) Loss of vision (2 yr)
Physical Findings:	Ovaries not palpable Absent sexual characteristics, short stature	Hemianopia. Reduced sexual hair. "Eunuchoidal". Normal testes	Hemianopia Normal sexual characteristics
Gonadotropins:			
Plasma FSH (or Urinary FSH)	Urinary "FSH" 200–300 MUU/L	32–64 mIU/ml (0.8–16)	1995 ng/ml (0–300)
Plasma LH		16 mIU/m. (2–30)	58 ng/ml (15–85)
Plasma Testosterone		235 ng/dl (400–1200)	390 ng/dl (300–1200)
Testosterone Suppression			Normal FSH & LH response
GnRH Stimulation			No FSH response Reduced LH response

*Normal range

TABLE II—*Continued*

Pituitary Tumors Associated with Increased Gonadotropins

Sperm Count; Gonadal Histology		34×10^6/ml (25% motile)	$85-150 \times 10^6$/ml (20% motile)
Other Pituitary Functions:			
GH	"Normal"	Reduced	Reduced
PRL		Normal	Normal
TSH	Normal	Reduced	Reduced
ACTH	Normal	Reduced	Reduced
Sex Karyotype	Chromatic Pos.	Chromatin Neg.	
Sella Turcica (Size) & Tumor Morphology		Chromophobe adenoma	
Tumor Function:		Immunofluorescent staining pos. with anti-FSH & anti-LH antisera. FSH produced by tumor in vitro.	Immunofluorescent staining pos. with anti-FSH & anti-LH antisera.
Miscellaneous:	Normal "FSH" Suppression after Estrogen		No FSH and LH response to clomiphene

Patient #:	8	9	10
Author (Reference)	Friend et al (14)	Cunningham & Hickins (12)	Kovacs et al (18)
Age/Sex:	33/M	55/M	61/M
History: (Duration)	Infertility (5 yrs) Loss of vision (2 yr)	Infertility (21 yrs) Impotence (2 yr) Headaches (2 mos)	Impotence (4 yr) Loss of vision (2 yr)
Physical Findings:	Hemianopia. Small testes. Reduced sexual hair. "Eunuchoidal"	Normal testes Reduced sexual hair	Normal sexual characteristics
Gonadotropins:			
Plasma FSH (or Urinary FSH)	360 ng/ml (0–300)	580 ng/ml (50–300)	15–21 mIU/ml (0.5–4.5)
Plasma LH	25 ng/ml (15–85)	<32 ng/ml (15–90)	3–5 mIU/ml (nl)
Plasma Testosterone	330 ng/dl (300–1200)	<22 ng/dl (300–900)	192 ng/dl
Testosterone Suppression	Normal FSH & LH response	No FSH & LH response	
GnRH Stimulation	No FSH response Reduced LH response	Increased FSH and LH response	Increased FSH response Normal LH response
Sperm Count: Gonadal Histology	Azospermia	Leydig cells sparse Hypospermatogenesis	
Other pituitary functions:			
GH	Reduced	Reduced	Reduced
PRL	Increased	Increased	Normal
TSH	Normal	Reduced	Normal
ACTH	Reduced	Reduced	Normal
Sex Karyotype	46 XY karyotype		
Sella Turcica (Size) & Tumor Morphology		Chromophobe adenoma	Chromophobe adenoma
Tumor Function:			Immunoperoxidase staining positive for FSH
Miscellaneous:		No FSH and LH Response to clomiphene	

TABLE II—*Continued*

Pituitary Tumors Associated with Increased Gonadotropins

Patient #:	11	12	13
Author (Reference)	Kovacs et al (18)	Peterson et al (21)	Burke and Marshall (11)
Age/Sex:	45/M	30/M	35/F
History: (Duration)	Impotence (1 yr) Loss of vision (1 yr)		Secondary amenorrhea (3 yr)
Physical Findings:	Hemianopia Normal sexual characteristics	Normal testes "Eugonadal"	Normal sexual characteristics
Gonadotropins:			
Plasma FSH (or Urinary FSH)	40–53 mIU/ml (<15)	2 mIU/ml (2–10)	
Plasma LH	6–9 mIU/ml (Normal)	207 mIU/ml (2–20)	12 mIU/ml (1.8–41) (Urinary LH 853 mIU/hr (90–350))
Plasma Testosterone	234 ng/dl	1500 ng/dl (300–1000)	
Testosterone Suppression			
GnRH Stimulation		Increased LH & α-subunit	
Sperm Count: Gonadal Histology		Azospermia; marked Leydig cell hyperplasia, decreased spermatocyte maturation	No ovarian follicles & corpora albicans
Other pituitary functions:			
GH	Normal	Normal	Normal
PRL	Normal	Increased	Normal
TSH	Normal	Normal	Normal
ACTH	Normal		Normal
Sex Karyotype			46 XX Karyotype
Sella turcica (Size) & Tumor Morphology	Chromophobe adenoma	Chromophobe adenoma	Tumor at sellar tomography only
Tumor Function:	Immunoperoxidase staining positive for FSH	LH & α-subunit produced by tumor in vitro	
Miscellaneous:		5αDHT androstenedione & 17αhydroxyprogesterone incr. Incr. LH response to estrogen	

Patient #:	14	15	16	17
Author (Reference)	Snyder & Sterling (22)	Demura et al (13)	Kovacs et al (18)	Nicolis et al
Age/Sex:	51/M	51/M	57/F	58/M
History: (Duration)	Impotence (1 yr) Loss of vision (1 yr)	Loss of vision (1 yr)	Secondary amenorrhea (20 yr). Loss of vision (1 yr).	Impotence (6 yr)
Physical Findings:	Hemianopia. Normal sexual characteristics. Testes 7 cms long	Hemianopia Normal sexual characteristics	Hemianopia	Normal sexual characteristics Small testes
Gonadotropins:				
Plasma FSH (or Urinary FSH)	30–53 mIU/ml (5–15)	176–295 mIU/ml (27 ± 7)	36.6 mIU/ml (8–50)	31 ± 2.5 mIU/ml (5–25)
Plasma LH	24–26 mIU/ml (5–15)	35–67 mIU/ml (17 ± 4)		58 ± 8.5 mIU/ml (16–30)
Plasma Testosterone	1380–1485 ng/dl (400–1200)	580–691 ng/dl (520 ± 62)		802 ± 28 ng/dl (300–1200)
Testosterone Suppression		LH response only		

TABLE II—*Continued*
Pituitary Tumors Associated with Increased Gonadotropins

GnRH Stimulation	Increased FSH response, normal LH response	No FSH and LH response	Increased FSH & LH response	Normal FSH and LH response
Sperm Count: Gonadal Histology		46 × 10^6 ml; normal testicular biopsy		Leydig cell hyperplasia tubular fibrosis & hyalinization.
Other pituitary functions:				
GH	Reduced	Reduced	Reduced	Normal
PRL	Increased	Normal	Increased	Normal
TSH	Normal	Normal	Normal	Normal
ACTH	Reduced	Normal	Normal	Reduced
Sex Karyotype				46 XY Karyotype
Sella Turcica (size) & Tumor Morphology	Chromophobe adenoma	Chromophobe adenoma with 10% eosinophil cell	Chromophobe adenoma	19 × 13 mm
Tumor Function:		LH & FSH produced by tumor in vitro	Immunoperoxidase staining positive for FSH & LH	
Miscellaneous:	Increased plasma DHT and "Free" T	Pituitary irradiation (8 yr) No FSH & LH response to estrogen	Abdominal irradiation for Hodgkin's disease (20 yrs)	Increased urinary bioassayable gonadotropins. FSH suppressed by estrogens

(31) and Caughey (32) first postulated that some pituitary tumors may arise in humans because of failure of the endocrine target glands. Their suggestion followed reports that ablation of the gonads (33) and of the thyroid (34) induced pituitary hyperplasia and pituitary tumors in experimental animals.

It has since been established that TSH and ACTH producing pituitary tumors do indeed occur in humans with longstanding thyroid and adrenal failure. (7, 9). The relation between primary hypogonadism and the development of gonadotropin producing pituitary tumors in humans is less clear. To our knowledge, macroscopic pituitary adenomas have not been reported in patients with one of the recognized syndromes of primary hypogonadism (for example, Klinefelter's and Turner's syndrome, anorchia, castration, pseudohermafroditism). Samaan et al (35) have recently found that patients with the Klinefelter's and the Turner's syndromes frequently have enlarged sellae turcicae, and/or localized abnormalities of the sellar contour suggestive of microadenomas. The sellar enlargement was modest (1330 to 1505 mm^3; normal up to 1092 mm^3) and the diagnostic value of the localized radiographic abnormalities has been subsequently questioned (36). In further contrast to the patients reviewed here, Samaan's patients had no visual field defects and no evidence of hypopituitarism. The findings of Samaan et al (35) appear to agree with older reports of moderate sellar enlargement in men castrated at a young age (37, 38), and with the report of Burt et al (39) that the pituitaries of 17 men with clinical Klinefelter's syndrome weighed 0.75 ± 0.15 gm (S.D.) as compared to 0.67 ± 0.14 gm in normal men (40). None of these 17 pituitaries contained macroscopic or microscopic tumors. These combined observations suggest that pituitary hyperplasia and/or microadenomas probably occur in patients with longstanding primary hypogonadism.

It seems reasonable to expect that like in the experimental animal (33), the pituitary hyperplasia and the microadenomas may sometimes progress to form macroscopic pituitary tumors. However this does not seem to occur frequently. Only about one half of the patients reviewed here had evidence of hypogonadism. In only one of these patients (case 16), was there satisfactory evidence that the hypogonadism was primary since her ovaries were irradiated twenty years before she developed signs of a pituitary tumor. None of the remaining patients was clearly diagnosed as having a recognized syndrome of primary hydrogonadism. Since gonadal failure is frequently the first manifestation of an "nonfunctioning" pituitary adenoma it cannot be stated with certainty whether or not the hypogonadism had preceded the development of the pituitary adenoma.

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Near Fatal Laetrile Intoxication: Complete Recovery with Supportive Treatment

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Abstract

We report an 18-year-old man, a follower of the "nutritional and metabolic antineoplastic diet," who developed near fatal laetrile intoxication following ingestion of three grams (30 tablets) of laetrile. After a clinical course marked by pulmonary edema and metabolic acidosis, he recovered completely with intensive supportive treatment.

More than 50,000 cancer patients consume over one million grams of laetrile each month (1). In spite of this widespread use, only seven published case reports have documented laetrile toxicity (2-7). We report a patient who developed near fatal laetrile intoxication after ingesting three grams (30 tablets) of laetrile. His clinical course was marked by pulmonary edema and lactic acidosis followed by complete recovery with intensive supportive treatment.

Case Report

An 18-year-old white man was brought to the Mount Sinai Services-City Hospital Center at Elmhurst on December 17, 1980, deeply comatose, cyanotic, diaphoretic, with dilated pupils, a blood pressure of 60/0 mm Hg, a pulse rate of 130 per minute, and shallow respirations of 12 per minute. No unusual breath odor was detected. Initially the chest was clear, but later both inspiratory and expiratory rales were heard. Examination of the heart revealed no murmurs or gallop. The liver was enlarged 3 cm below the right costal margin, the spleen, 2 cm below the left costal margin. Stomach aspiration revealed fragmented tablets. Gastric lavage with activated charcoal, and mechanical ventilation with 100% oxygen were instituted upon admission. A hemogram revealed a normal hematocrit and white blood cell count, 16,300/μL with a normal differential count. Ketones were not present in the urine. The serum sodium was 138 mEq/L, potassium, 4.7 mEq/L, chloride, 101 mEq/L, and total carbon dioxide, 8 mEq/L. An anion gap of 29 (normal 8–12) mEq/L was found. The BUN was 11 mg/dL, glucose, 235 mg/dL, SGOT, 111 mU/ml, SGPT 98 IU/L, and total bilirubin 1.7 mg/dL. Arterial blood gases while the patient was receiving 100% oxygen demonstrated severe metabolic acidosis with a pH 7.06. The electrocardiogram revealed marked right axis deviation and marked ST segment depressions in leads V2 to V6, suggestive of myocardial ischemia. The chest x-ray following intubation showed normal heart size and a bilateral diffuse alveolar pattern consistent with pulmonary edema. Intravenous fluids and dopamine were given for hypotension. The serum bicarbonate concentration increased from 7 to 14 mEq/L five hours after 267.6 mEq of sodium bicarbonate were given. Five hours after admission the patient became alert and extubated himself. While he was receiving oxygen via a 60% venturi mask, the PaO_2 was 72 mm Hg, $PaCO_2$, 32 mm Hg, bicarbonate, 14 mEq/L and pH, 7.22. Diuresis with furosemide cleared the chest of persisting rales.

It was subsequently learned that the patient, a chronic schizophrenic with paranoid delusions and cancerophobia, was following "the nutritional and metabolic antineoplastic diet" of laetrile proponents. A total of 55 substances, including megadoses of vitamins (A, B, C, D, E, K), minerals (calcium, iron, magnesium, phosphate, selenium, zinc), proteins, amino acids, fatty acids,

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natural RNA/DNA, digestive enzymes, other health foods such as herb tea, bone meal, alfalfa sprouts, brewer's yeast, and garlic had been taken intermittently for one year. On the day of admission, he ingested 30 tablets of laetrile (three grams) plus other substances in his usual daily doses and, within one-half an hour, collapsed. A routine toxicology screen of blood and gastric contents was negative. Sequential blood gas studies are shown in Table I. The chest x-ray cleared, and the electrocardiogram showed disappearance of the ST depressions the following day. After recovery, the patient received in-patient psychiatric care. A liver-spleen scan done one week after admission showed a slightly enlarged spleen and normal sized liver. Within two months the liver and spleen were not palpable and the liver enzymes returned to normal.

Discussion

Our patient attempted suicide by ingesting 30 tablets (three grams) of laetrile. He was comatose and hypotensive on admission. The severe metabolic acidosis with a large anion gap was most likely lactic acidosis. The ischemic electrocardiographic ST segment changes were probably due to hypoxia, and the pulmonary edema which responded promptly to furosemide was most likely cardiac in origin. In the absence of other intoxicating agents or causes, the constellation of clinical signs and symptoms strongly suggested acute cyanide poisoning; unfortunately cyanide blood levels were not measured.

Our patient believed in the "nutritional and metabolic antineoplastic diet" (8) and regularly took laetrile, megadoses of vitamins, minerals, digestive enzymes, and other health foods to prevent cancer. On admission to the hospital he was found to have hepatosplenomegaly and abnormal liver enzymes whose disappearance two months after stopping all health foods suggested either vitamin A intoxication or chronic cyanide poisoning.

TABLE I

Blood Gases and Anion Gap Following Laetrile Ingestion

Time	pH	PaO_2 mm Hg	$PaCO_2$ mm Hg	HCO_3 mEq/L	F_iO_2 %	Anion Gap mEq/L
Admission	7.06	220	22	7	100	29
Hour 1	6.94	67	42	10	35	—
Hour 2	7.01	119	36	10	60	—
Hour 3	7.14	102	30	11	60	—
Hour 5	7.22	72	32	14	60	—
Hour 10	7.42	78	33	22	60	—
Hour 12	7.45	55	32	23	21	—
Hour 24	7.39	101	34	21	21	14

Laetrile is a trade name for amygdalin, a cyanogenic glycoside naturally present in the kernels of apricot pits and many other plants. A gram of laetrile contains 60 mg of cyanide and the average fatal dose of cyanide is 50-60 mg (8). The release of cyanide, however, depends entirely on availability in the gastrointestinal tract of microbial beta glucosidase. Megadoses of vitamin C and the vegetarian diet recommended by laetrile proponents may increase the release of cyanide (9).

Cyanide causes tissue hypoxia by binding very tightly with cytochrome oxidase and inhibiting electron transfer to oxygen and ATP formation in the mitochondria. This causes a shift from oxidative phosphorylation to anaerobic glycolysis. The end product of anaerobic glycolysis is lactic acid, which gives rise to a significant anion gap. The degree of anion gap widening correlates with the severity of cyanide poisoning.

Treatment of laetrile overdose is identical to that of cyanide poisoning. The accepted regimen consists of sodium nitrite and sodium thiosulfate (10). However, the usefulness of this combination has been questioned. A more promising and less toxic antidote is hydroxocobalamin, which combines with cyanide to form cyanocobalamin (10). Graham and colleagues (10) emphasized the importance of supportive care. Our patient responded to intensive supportive treatment including fluids, bicarbonate, dopamine, furosemide, and assisted ventilation with oxygen. We agree with Graham that a patient can recover from cyanide poisoning when supportive treatment is instituted promptly.

There were two fatalities among the seven published case reports of laetrile toxicity (5, 6). Blood levels of cyanide were measured in five of seven cases. Blood levels, however, do not necessarily reflect extent of intoxication since cyanide is rapidly expired and detoxified in the body. The best parameters of laetrile intoxication are the patient's clinical condition and the degree of anion gap widening. Our patient survived severe cyanide poisoning. All physicians should be aware of the clinical features and treatment of laetrile toxicity.

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Comments on the Anniversary of the Description of Hodgkin's Disease

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Thomas Hodgkin introduced his discussion of the condition we now know as Hodgkin's disease with modesty characteristic of his entire life, indicating, in his first sentence, that his findings were "probably familiar to many practical morbid anatomists" (1). One hundred and fifty years later we recognize that there is, indeed, some evidence that Hodgkin's suspicions were correct (2–4). Hodgkin was informed of Malpighi's work after his paper was presented at the January, 1832 meetings of the Medical-Chirurgical Society of London and referred to it in the published version of his manuscript (1). Despite this, it is clear that Hodgkin's scholarly report of seven patients is truly original and that he has greatly influenced the evolution of the understanding of disease processes.

Hodgkin's paper continued the emphasis of the thesis he submitted to satisfy the requirements for graduation from the Edinburgh medical school (5). He showed the interrelationship of the lymph nodes (absorbent glands) and the spleen in terms of normal function, and, in 1832, of disease. Hodgkin's studies helped to establish the concept of the lymphoreticular system. In commenting on case VI, Hodgkin noted that the patient's lymph node enlargement was "concomitant to the idiopathic interstitial enlargement of the absorbent glandular structure throughout the body." And, later in the paper, he reflects on: "further confirmation of my suspicion that a connection exists between the glandular derangement of which I have been speaking, and the state of the spleen."

Hodgkin recognized the neoplastic nature of the condition he studied and did not hesitate to indicate clearly that he was describing a condition distinct from usual forms of lymph node disease, which were inflammatory: "this enlargement of the glands appeared to be a primitive affection of those bodies, rather than the result of an irritation propagated to them from some ulcerated surface or other inflamed texture." Clinical experience, as well as morphologic studies, supported his view: "unless the word inflammation be allowed to have a more indefinite and loose meaning then is generally assigned to it, this affection of the glands can scarcely be attributed to that cause, since they are unattended with pain, heat, and other ordinary symptoms of inflammation."

There was no recognition, in his own time, of the importance of his observations. His doctoral thesis was commended only for the quality of the Latin (6) and his 1832 paper was not even mentioned in the summaries of his "most valuable" (7) and "most important" (8) works recorded in the obituary notes following his death. Hodgkin, himself, never returned to this subject and never counted it as his most significant contribution.

In spite of his skills at microscopy (9), he never subjected the lymphoid tissues he examined to histologic study and it was only in 1926 that Hodgkin's cases II, IV, and VII were confirmed as being that which we now recognize as Hodgkin's disease (10). It does not, in any way, diminish the significance of his observations and interpretations to note that the other cases included examples of non-Hodgkin's lymphoma, tuberculosis, and syphilis. These conditions may, even today, with excellent tissue processing and microscopy, be confused with Hodgkin's disease (11).

The 1832 paper is the beginning of our understanding of the lymphoreticular malignancies and can be regarded as the first step in our recognition of the immune system and its disorders. However, this seminal contribution might well have been completely lost had it not been for Samuel Wilks, a successor to Hodgkin at Guy's Hospital and a great physician who demonstrated uncommon generosity. Hodgkin's paper was in a relatively obscure medical journal. Richard Bright briefly alluded to Hodgkin's work in a discussion of abdominal tumors, and emphasized that the condition "varies from the more usual

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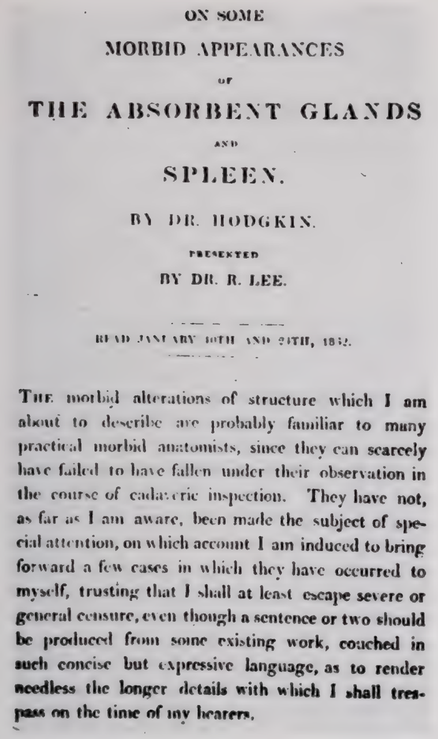

ON SOME
MORBID APPEARANCES
OF
THE ABSORBENT GLANDS
AND
SPLEEN.

BY DR. HODGKIN.

PRESENTED
BY DR. R. LEE.

READ JANUARY 10TH AND 24TH, 1832.

THE morbid alterations of structure which I am about to describe are probably familiar to many practical morbid anatomists, since they can scarcely have failed to have fallen under their observation in the course of cadaveric inspection. They have not, as far as I am aware, been made the subject of special attention, on which account I am induced to bring forward a few cases in which they have occurred to myself, trusting that I shall at least escape severe or general censure, even though a sentence or two should be produced from some existing work, couched in such concise but expressive language, as to render needless the longer details with which I shall trespass on the time of my hearers.

form of malignant disease (12). In 1856, Wilks independently described the same disease Hodgkin had recognized (13). After writing his paper, Wilks learned of Bright's citation and read Hodgkin's publication. Wilks wrote a second paper on the topic, in 1865, and, using the designation "Hodgkin's disease" for the first time, gave full credit to "Dr. Hodgkin, who was the first, as far as I am aware, to call attention to this peculiar form of disease" (14).

The name of Thomas Hodgkin has, since that time, become an integral part of the lexicon of medicine and will certainly remain so, at least until the time when Hodgkin's disease ceases to be enigmatic in terms of its etiology and pathogenesis. When that disease is finally understood, the name could well become replaced by a more scientifically sound appelation and Thomas Hodgkin might be forgotten. This would, however, be tragic, for Hodgkin's fine study is but one small part of the enormous contribution he made to science and to humanity.

Hodgkin first described aortic insufficiency in 1827 (15), five years before Corrigan (16). He accurately documented the nature and complications of appendiceal perforation (17), more than 50 years before Fitz (18). Hodgkin recognized arteriosclerotic disorders (19, 20), and alcoholic cardiomyopathy (21). He was probably the first to promote the concept of the resident physician as a means to improve postgraduate medical training, while exhorting his medical school colleagues to encourage more preclinical training in the basic sciences for the undergraduate student (22, 23). He is most likely responsible for the introduction, and certainly for the promotion, of the Laennec stethoscope into the practice of medicine in England (24). Few have been as ardent as Thomas Hodgkin in supporting the usefulness of the autopsy in the study of human disease (25). Hodgkin developed the magnificant pathology museum at Guy's Hospital, now known as the Gordon Museum.

Thomas Hodgkin was greatly respected as a physician, scientist, and teacher (26), but his professional achievements pale when compared to his humanitarian pursuits (27). Following his disappointment at not being appointed "Physician to Guy's Hospital" (28), Hodgkin devoted a greater proportion of his time to philanthropic activities. He denounced conditions of poor sanitation in London, overcrowding, lack of adequate fresh air in the city, and the employment of children as chimney sweeps and factory workers. He vigorously promoted vaccination for smallpox. He urged his fellow physicians to be mindful of their responsibilities to care for the poor (29). He was a linguist, ethnologist, anthropologist, geologist, one of the leaders of the Royal Geographical Society, and a founder of the University of London. Thomas Hodgkin was a most sincere, most committed, and most vociferous opponent of slavery and had a passionate interest in the fate of primitive and oppressed people, particularly North American Indians and Negros (30–32); he was a founder of the Aborigines Protection Society, devoted mostly to the aboliton of slavery. Indeed, he showed his concern for the plight of his fellow human beings, whether they were in London, Europe, Asia, Africa, or the United States, and his last years were completely devoted to self-sacrificing activities to better the condition of the poor, to abolish slavery, and to relieve the persecution of the Jews in Africa.

Hodgkin's great and close and devoted friend was Sir Moses Montefiore. Together, Hodgkin, a steadfast Quaker, and Montefiore, a rigidly observant orthodox Jew, travelled widely, attempting to improve the status of the many who lived desperate lives. In 1866 they went to the Holy Land to aid distressed Jews and Arabs who were in the mist of a cholera epidemic. Hodgkin became ill soon after disembarkation. After an exemplary life devoted to his art and his fellow man, Thomas Hodgkin died in Jaffa.

In this, the 150th anniversary year, we must note that the nature of Hodgkin's disease remains almost as much a mystery at it was in 1832 (33). Thomas Hodgkin's interests and achievements, only some of which were recorded here, are extraordinary in their scope and in their influence on his and our society. Hodgkin is still buried in the old Anglican cemetery of the ancient city of Jaffa. Sir Moses had an obelisk erected at the burial site; it bears the inscription "Humani nihil a se alienum putabit" (nothing human was foreign to him) (34).

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Neurologic Complications of Open Heart Surgery

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Coma, stupor, hemiplegia, monoplegia, cranial nerve palsy, confusional states, seizures, and psychiatric symptoms have all been described as neurologic complications of open heart surgery. The great variation of these complications, encompassing the entire spectrum of encephalopathic phenomena, can be readily ascribed to the diffuse nature of injury sustained by the brain of the cardiac surgical patient undergoing a procedure, performed of necessity, known as cardiopulmonary bypass.

Surgical procedures requiring complete cessation of the heart's activity and thereby its oxygen pumping capability awaited the advent of cardiopulmonary bypass, a technique by which extracorporeal oxygenation of the patient's blood could be accomplished. The delivery of oxygen to the brain is an absolute physiologic necessity because the brain, beyond any other body organ, has an excessive appetite for oxygen, consuming 3 ml to 5 ml of oxygen/100gm/minute. This amount is more than 20 percent of the total body oxygen consumption despite the fact that the brain accounts for only 2.5 percent of total body weight. Obviously, the events that alter cerebral perfusion in the course of bypass and adversely affect the regional distribution of blood flow to the brain will influence the outcome of the procedure. Technical factors related to viscosity, gas-hemoglobin affinity, gas tensions, hematocrit, and pH may ultimately be related to postoperative cerebral dysfunction. Such technical discussion and even the mechanical process of bypass are beyond the scope of this article and the reader is referred to both the cardiac-surgical literature and the book "Post-Operative Care of the Cardiac-Surgical Patient" edited by Robert Litwak for a fuller discussion and overview (1).

Originally, anywhere from 19% to more than 50% of patients undergoing open heart surgery with bypass were reported as having manifested neurologic complications, an incidence of neurologic morbidity that far surpassed the neurologic sequelae of almost any other type of major surgery (2–4). As understanding of the physiologic implications of bypass became more clarified, the incidence of neurologic complications lessened (5, 6). Efforts were made to counteract the deleterious effects of bypass, with both mechanical and chemical agents, as well as the use of prosthetic valves which were less likely to be a source of cerebral emboli. The success of these applications together with technical advances in cardiopulmonary operative technique have mitigated the incidence of postoperative neurologic morbidity today. The use of filters in operative lines, the use of intraoperative administration of prostacycline to preserve platelets and platelet function, better valve design, as well as cardioplegia have all contributed to a better neurologic postoperative prognosis (7–9).

A variety of lesions have been demonstrated on neuropathologic examination of open heart surgical patients. Approximately 25 percent of patients clinically identified as having sustained cerebral insults expire and gross hemorrhages, infarcts, diffuse bilateral changes as well as areas of cortical infarction have been seen in their brains (10). Surprisingly, the brains of patients who are equally afflicted from a clinical point of view may appear normal. Microscopic changes such as emboli, acute hemorrhages, and diffuse and focal neuronal necrosis have been seen in up to 85 percent of the entire postmortem cardiac surgical population which includes patients who have never manifested neurologic signs or symptoms indicating that the clinical expression of this disorder does not correlate with the pathologic findings in many cases. Thus Hill et al in 1969 postulated that the changes visualized were due to fat

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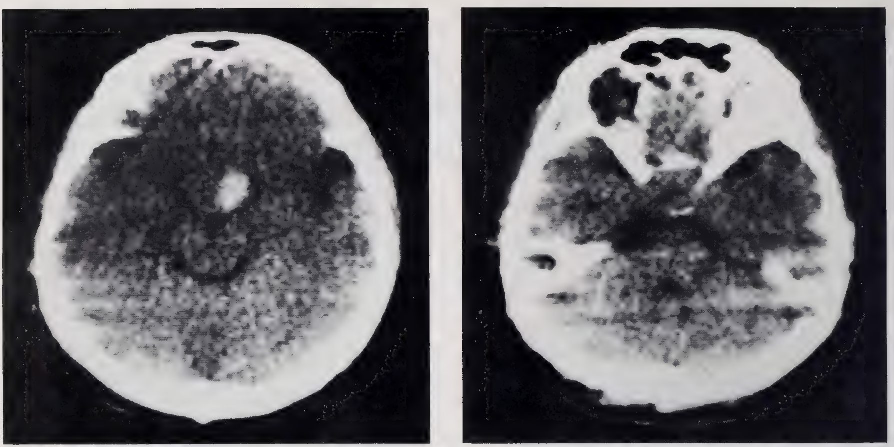

Computerized tomography of the head without contrast enhancement showing a large suprasellar mass lesion, the half of which has an increased density representing a hematoma within a chromophobe adenoma confirmed at surgery (Fig. A). There is also enlargement of the sella turcica with erosion of both posterior clinoids and the anterior clinoid along with the dorsum sella (Fig. B).

(Courtesy of Y. P. Huang, M.D., Department of Neuroradiology, Mount Sinai Hospital)

emboli and that the vast majority of patients undergoing open heart surgery and bypass were affected (11).

Approximately 80 percent of neurologic complications are evident at the time the cardiac surgical patient is first examined in the recovery room. Further complications may be encountered as a consequence of subsequent cardiac or renal failure later in the patient's course. Rapid identification of those patients with neurologic dysfunction is mandatory since there is a high incidence of seizures in such patients, no doubt related to the diffuse and irritative nature of the pathology. Experience has indicated that approximately one out of three noncomatose neurologic patients will seizure in the immediate postoperative period. Occasionally, a patient with no other evidence of neurologic dysfunction will seizure as the sole indication that the brain has been damaged by surgery and bypass.

Coma remains the most serious neurologic problem seen in cardiac surgical patients. Failure to awaken following the conclusion of the operative procedure carries a grave prognosis. In such cases, however, it is wise to delay a final prognosis until a series of flat electroencephalographic tracings are obtained 24 hours apart. An occasional patient may be over reacting to agents used in the induction of anesthesia or the anesthesia itself and the use of appropriate antagonists should be considered.

To further complicate diagnosis, there are other patients with preexisting intracranial disorders unbeknownst to the surgical staff who undergo bypass surgery and become acutely affected by heparinization, a procedure attendant on the performance of surgery with bypass. One such patient developed a pituitary apoplexy when his undiagnosed pituitary adenoma hemorrhaged during his cardiac surgery requiring craniotomy a few days later to preserve his vision. Furthermore, the hypotension required by bypass which is performed at approximately 80 mm of pressure may provoke symptomatology due to undiagnosed extracranial obstructive lesions and may result in stroke.

Every effort should be made to identify those patients with pre-existing neurologic or vascular lesions prior to surgery to forestall such catastrophies. Noninvasive vascular screening studies are recommended in patients if cerebrovascular disease is suggested and angiography and endarterectomy should be considered. It is still too early to say for sure as to whether repair of obstructive extracranial vascular lesions will influence the outcome of such patients following surgery performed with bypass.

In general, despite the varied and worrisome neurologic phenomena exhibited by cardiac surgical patients, the pathophysiologic insult to the brain is self limited in most cases and usually reversible. The therapy of the neurologic complications of open heart surgery is no more than the therapy of the patient with stroke or seizure. Good medical attention, physiotherapy, anticonvulsant agents for the first ten postoperative days, and tincture of time will usually result in a satisfactory outcome. Subsystem dysfunctions already alluded to will adversely affect the neurologically afflicted patient and prolong neurologic recovery. The use of steroids in unresponsive patients may be attempted but their value has yet to be demonstrated. In view of the dire prognosis associated with the comatose patients, steroid use may be tempting.

A psychotic state characterized as postcardiotomy delirium originally received a great deal of attention in the early days of open heart surgery and was felt to be a nonorganic manifestation of cardiac surgical patients to the stress of postoperative care, sleep depriviation, and the repression of anxiety associated with the procedure of opening the patient's heart. This state was manifested by the appearance of illusions, hallucinations, and paranoid elaborations and usually appeared following a two- to five-day lucid interval (12). It was later ascertained that psychologic and environmental manipulation of themselves had not resulted in a decrease of these symptoms and that an organic basis was more likely (13).

In summary then, it must be concluded that most instances of neurologic dysfunction following open heart surgery result from both predisposing and operative factors, the latter largely having to do with current methods of cardiopulmonary bypass.

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Psychiatric Reactions to Colectomy: A Literature Study

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Colectomy has been one of the more commonly performed major surgical procedures for several decades, but it is only in the past 30 years that physicians have looked beyond the physical problems of colectomy patients. In 1947, Dukes (1) described 100 permanent colostomy patients and emphasized the importance of a supportive spouse and home to good "adjustment." He noted patient anxiety about eventual invalidism, and depression in the postoperative period. In 1948, McLanahan and Gilmore (2) found that over 50% of their study population had some curtailment of activities, but these were not specified. Ewing (3), in 1950, found a serious restriction of social activities in a group of 20 patients. These early studies showed increasing awareness by physicians of the psychic trauma and impairments following colostomy; however they did not provide controlled comparisons of function before and after surgery, nor did they identify specific areas of impaired function and explain how these impairments actually disrupted the patients' lives. One of the first studies to do so, and a turning point in the field, was conducted by Sutherland et al in 1952 (4).

Sutherland et al studied a group of 76 patients who had had colostomies for at least five years prior to the study and were considered free of recurrence of the cancer. Specifically, they examined the roles of irrigation and spillage in total functioning, the ultimate effects of colostomy on work, social, family, and sexual function, and patient reactions to the surgical experience itself.

Because childhood attainment of sphincter control is fundamental to the process of human socialization, the removal of the rectum is likely to result in severe emotional and social disruption. Sutherland et al found that irrigation replaces sphincter control. They noted that many patients develop compulsive practices related to irrigation as a defense mechanism in an attempt to regain the lost control. Certain of these associated procedures, to which the patients rigidly adhere, seem to be invested with "magical powers" (4) geared to decrease anxiety, and other life functions are often arranged around the irrigation ritual.

Spillage (accidental leakage of feces at an inopportune time) was found to represent to the patient a failure to regain the lost control; it results in massive functional impairments, especially social participation. Spillage is always accompanied by a severe loss of self-esteem and depression, often approaching suicidal level. Food becomes important to the patient as a means of regulating bowel function, with constipating foods taken to avoid spillage while laxative foods are taken prior to irrigation (4).

The study indicated that the relationship of the colostomy patient to his family depends mostly on what existed prior to the surgery. If the prior relationship was good, then it becomes a support and a source of strength for the patient after surgery. Pre-existing tensions tended to worsen and, in these cases, family relationships deteriorated after surgery (4).

Sexual function is also affected by the colostomy. The extensive resection required for cancer patients may often sever neural pathways involved in sexual function, and many men are totally or partially impotent following the operation (5). As with general family relationships, marital problems worsened. Among women, pre-existing frigidity continued after surgery with the colostomy used as a justification to stop intercourse. Colostomy was found to be a deterrent to remarriage or new sexual contact (4).

The work function of colostomy patients was found to be inversely related to the degree of the affective impairment. Some patients resumed full work, with anxiety about the possibility of spillage, while most curtailed their work to some degree, out of fear of over-exertion, injury to a weakened body, or accidental spillage. Participation in community social events, and travel were more impaired than work function; they are curtailed partly or completely out of fear of spillage, odor, or noise resulting in social unacceptability or due to the spending of free time on irrigation (4).

The reaction of the patient to the surgical expe-

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[*] This work was completed during Dr. Barr's third-year in medical school, Mount Sinai School of Medicine (CUNY).

rience has a bearing on later functioning. Preoperative fear of bodily injury virtually always causes some affective disorder–despair, anxiety, confusion, and/or panic. After surgery, the patient may become convinced that terrible injury has occurred. This commonly leads to a sense of weakness, reflecting a loss of confidence in the body, or to overt depression, associated with eating and sleeping problems (4). The first sight of the stoma is always a shock, and the first attempt to irrigate is quite upsetting, resulting in depression that is often worse in patients who have had more severe preoperative disorders. It was found that great importance is attached to contacts with the surgeon and other hospital personnel. Warm and supportive doctor and nurse relationships are strong motivations in creating a positive outlook. It was noted that some patients tried harder to help themselves after the surgery to win the approval of nurses involved in their care (4).

Sutherland et al closed their report with some recommendations for the management of colostomy patients, because it was felt that (except for male impotence) most serious curtailments of activity are psychologic in nature. These may be of special interest to the surgeons and nursing staff concerned with the care of these patients. The authors suggest first that psychologically oriented management should begin even before the surgery is performed. The surgeon should be aware that the patient's anxiety is the outward manifestation of fear of major bodily injury or death occurring during surgery; if panic, confusion, or despair occur, psychiatric intervention may be necessary. Also, the patient may have other problems, indirectly related to health concerns (such as medical costs and future ability to earn a living) which may heighten stress. The surgeon is the most important figure in the patient's defenses against the dreaded anticipation of injury or death, and the surgeon can aid these defenses by displaying a friendly and protective attitude. Care should be taken to choose what information is given regarding the surgery, and how it is conveyed to the patient (4). The authors also noted that personal contact with a familiar physician preoperatively (if possible, at the time of anesthesia) may help.

In the postoperative period, the surgeon can be especially important in encouraging the patient. The support provided may be used as a reward to the patient for the restoration of functions, thereby preventing needless limitations of activity, dispelling fears of incapacitation, and decreasing the chances of reclusion. Surgeons and their staff should be aware that open expression of resentment against them is considered to be a helpful reaction which allows the patients to directly confront and resolve some of his anger (4).

Dispelling of physiologic misconceptions early on can resolve certain unfounded fears concerning the function of the new and unfamiliar anatomic arrangement. Experience has indicated that colostomy irrigation should be taught in frequently repeated lessons, with consistent information given at each lesson to avoid confusion. The patient is best helped if he has reviewed the procedure so thoroughly that he will not need to practice it much at home. This can prevent the often observed fixation to colostomy and irrigation. In addition, readying all the facilities needed for colostomy care at home prior to the patient's release, as well as having the family prepared by a social worker, may ease the patient's return to normal life activities (4). The patient should be prepared for the possibility of future physical problems, and be reassured that they will be watched for and tended to as necessary.

Finally, Sutherland et al add that when problems related to the functioning of the stoma cannot be explained by detectable physical abnormalities, the physician should consider the possibility of a psychologic etiology. When other life functions are disturbed, psychiatric intervention may prove valuable, and more beneficial if the aid is received early during convalescence (4).

In 1956, Dyk and Sutherland reported on the adaptation of spouse and other family members to the colostomy patient (6). It was found that the marital relationship is a powerful adaptive force in the patient's life. Some differences were noted between the responses of male and female patients, as well as in the reactions to them by husbands versus wives. Men tend to rely on their wives as nurses during the convalescent period at home, while the female patients are more likely to prefer the assistance of another woman rather than depend on their husbands for nursing care. Wives of colostomy patients are more disparaging and negative about the stoma than are husbands of such patients. Indeed, husbands are more supportive and less bothered by the stoma. The perception of colostomy as physically unacceptable to the spouse was greater in women than in men (6).

In 1957, Orbach et al (7) provided a detailed illustrative report on colostomy patients' fears and the defensive adaptations utilized in response to the loss of anal sphincter control. They concluded that compulsive, ritualized techniques of irrigation, special eating habits, and other daily routines are developed as a replacement for lost sphincter control and as defenses against what is perceived to be the possibility of "contamination"

(7). Women with colostomies who had been greatly concerned with personal hygiene and the cleanliness of their homes prior to surgery, spend a long time in irrigation and introduce large amounts of water into their colostomies. This is interpreted as an attempt to prevent contamination that presumably follows loss of control over the evacuation of substances assumed to be poisonous to the body (8). These compensatory mechanisms may at times become dominant, and lead to impairment affecting many other important life functions (7).

Kolb (9), in 1959, reported that a sudden change in body image, that is, the presence of a stoma, inevitably causes anxiety. In addition, the loss of a valued body part results in mourning similar to that of loss of a significant person (9).

Orbach and Tallent (10), in a follow-up study in 1965 of patients who had had stomas for five to ten years, determined that virtually all feel that their bodies have been altered in a destructive way. Often, patients are bothered that they must "face people with a substitute anus in front" of their bodies (10). Many worry about the fragility of the body, weakness, and the possibility of backwash and contamination, all of which contribute to depression and feelings of inadequacy. When these feelings are strong, a common defense is to limit activities and social contacts (10).

In 1967, Katona (11) re-emphasized that the colostomy will control the patient unless he learns to control irrigation and spillage, and it is recommended that the process of retraining a patient to control bowel function is best accomplished as soon as possible after the surgery, prior to returning home.

In 1968, Druss et al (12) described a study of patients who had undergone colectomy and ileostomy as treatment for severe, chronic ulcerative colitis. Despite concern about odor and the inconvenience of the ileostomy appliance, for many patients, other areas of functioning, such as social and sexual activities, are improved because they are freed of the debilitating chronic diarrhea and other abdominal symptoms (12). The concept of bodily worth and integrity that the patient retains following surgery, as well as the actual and imagined responses of the spouse or other significant people are, in their way, just as important to patient outlook as physical factors. Also, many patients feel that having more information before surgery is helpful. Ostomy Clubs are reported to be an excellent source of practical guidance and role models, and the first postoperative year is considered to be a crucial time for readjustment (12).

In 1969, Druss et al reported on a similar study in which cancer patients were examined, and their responses were compared to those of the ulcerative colitis patients. There are, of course, certain similarities between the two groups of patients. Both have lost their colons and anal sphincter control. Both defecate from the front of the body surface, through the stoma, which has been created by the surgeon resulting in a changed body image. Both patient populations experienced depression immediately after surgery, and felt a sense of mutilation due to the loss of an organ which had been necessary to conform to society's code of cleanliness (13).

However, there are also differences, both anatomic and psychologic, that are important to note. Firstly, the ulcerative colitis patients tend to be younger than the cancer patients, and therefore have different problems. Secondly, the operation for cancer is more extensive and damaging to neural pathways that are more frequently spared in the resection performed for ulcerative colitis (5). Also, the ulcerative colitis patient has an ileostomy, which is completely untrainable and necessitates the wearing of an appliance at all times, while the cancer patient's colostomy allows some retraining of bowel control and eventually may function without a bag (13). From a psychologic point of view, the ulcerative colitis patient has had surgery following a long history of a troublesome chronic disease which to begin with, often has a psychologic component. (Ulcerative colitis patients often are dependent personality types (12).) For these patients, the operation is often seen as a welcome relief and therefore is easier to adjust to. In contrast, colostomy resulting from surgery for rectal cancer is different; the patient has no previous chronic bowel problems and his acute disease is unassociated with any pre-existing emotional disturbances. In many ways, surgery is not regarded as an improvement (13). Most victims of carcinoma recognize and appreciate the value of the operation as a life-saving necessity, but they are faced with adjusting to a sudden, severe physiologic insult. At the same time, cancer patients must deal with the ever-present fear of recurrence of the tumor and the threat of death, while ulcerative colitis patients are relatively free of fear of recurrence after surgery (12, 13). Druss suggests that surgeons should be aware of the cancer patient as well as the ulcerative colitis patient, and he restates some of the recommendations for postoperative management that Sutherland had outlined 17 years earlier.

In conclusion, patients undergo colectomy either for cancer or chronic ulcerative colitis. Over the past 30 years, surgeons and psychiatrists have become increasingly aware that the anatomic changes induced by surgery can be entirely successful from a physical point of view and yet they may be a source of tremendous grief and conflict from an emotional aspect. The studies described in this limited literature study provide an overview of the evolution of the better understanding of these aspects of surgery. The surgeon should utilize these important recommendations for pre- and postoperative care to attain a better psychologic adaptation to a critically important but emotionally traumatic surgical procedure.

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Hypoglycemia Associated with a Large Histiocytic Lymphoma: Case Presentation and Literature Review

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Abstract

The case of an elderly insulin-receiving diabetic woman, with a massive retroperitoneal histiocytic lymphoma and severe hypoglycemia is reported. A review of the literature on non-β cell tumor hypoglycemia and the theories on its pathogenesis are presented with a discussion of the possible mechanisms involved in the production of hypoglycemia in this patient.

A 72-year-old Oriental woman was admitted to the Lenox Hill Hospital on June 16, 1979 with the chief complaint of abdominal pain for four days. She also complained of anorexia, weight loss, weakness, and abdominal fullness over the past two to three months. She had a 16-year history of diabetes mellitus and until recently was maintained on diet and 30 units of NPH insulin daily.

Six days prior to admission, she was brought by her family to the emergency room of another hospital because of weakness and severe mental confusion of acute onset. Her blood sugar then was found to be 15 mg/100 ml, and her symptoms were relieved completely by intravenous glucose administration. Following this, her insulin dose was decreased to 10 units of NPH for two days, after which the insulin was completely discontinued. She received no insulin for four days prior to and during the present admission. Her past medical history was significant for atherosclerotic heart disease with hypertension and congestive heart failure, as well as severe bradyarrhythmia necessitating a pacemaker insertion.

Physical examination revealed a responsive, poorly nourished, pale, elderly Oriental woman in considerable discomfort. A large, firm, fixed, nontender midabdominal mass was palpated extending from the midepigastrium to 5 cm below the umbilicus. The serum glucose on admission was 54 mg/100 ml. Fasting blood glucose values ranged from 20–54 mg/100 ml, and the patient had to be maintained on constant intravenous infusion of glucose, supplemented with a liberal oral intake of carbohydrates for symptomatic relief of hypoglycemia. Fasting insulin and proinsulin levels were unsuccessfully attempted because of the presence of antibodies in the patient's serum. Multiple serum samples were tested for "C" connecting peptide, growth hormone, somatomedin, cortisol, and ACTH levels and were all normal. Thyroid studies were normal as well. The patient's serum was tested for the presence of nonsuppressible insulin like activity (NSILA). This was found to be 65% of the normal control (normal 100 ± 50% of control). The glucagon, subcutaneous epinephrine, tolbutamide, and the arginine infusion tests were attempted but could not be completed inasmuch as the patient could not tolerate even a four-hour fasting.

Intravenous pyelogram, abdominal sonogram, celiac angiogram, and abdominal CT scan (Fig. 1) confirmed the presence of a large retroperitoneal avascular mass, compressing the left kidney and ureter and displacing the celiac vessels anteriorly. A liver-spleen scan revealed no metastases.

The patient's clinical condition deteriorated rapidly. On June 29, 1979, ten days after admission to the hospital, she had a cardiac arrest and expired. At autopsy, a 1400 gram retroperitoneal, fleshy, necrotic tumor was found (Fig. 2) with extension to the left kidney and with distant metastases to the mediastinal lymph nodes, bronchi, myocardium, vertebral bone and musculature. The pancreas appeared normal on both gross and

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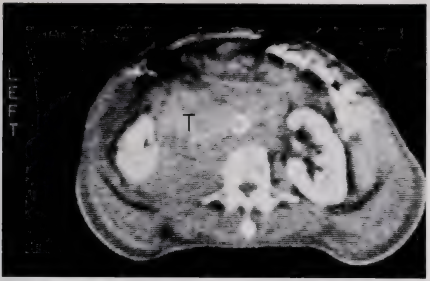

FIG. 1. Abdominal CT scan at the level of the lumbar vertebrae shows a large midline tumor mass (marked T) occupying the entire space between the two kidneys.

microscopic examination. The liver was notably free of metastases and showed adequate glycogen stores. Histologic examination of the tumor disclosed the presence of large anaplastic cells with large pleomorphic vesicular nuclei with multiple mitoses (Fig. 3); a reticulin stain showed fine reticulin fibers surrounding nests and individual tumor cells (Fig. 4), thus confirming the diagnosis of a diffuse, infiltrating histiocytic lymphoma.

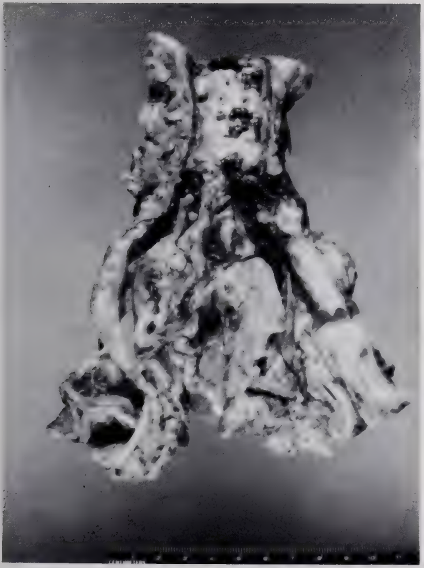

FIG. 2. Gross appearance of the tumor on the excised autopsy specimen. The abdominal aorta is cut open, and the tumor is seen as a large, fleshy mass in the midline.

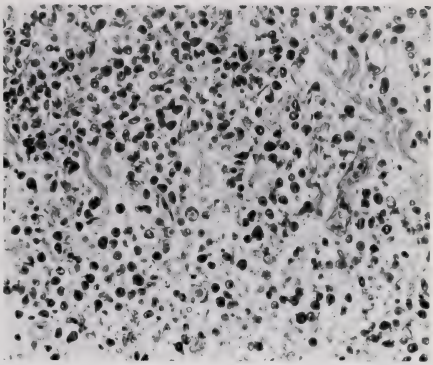

FIG. 3. Microscopic appearance of the tumor, showing large anaplastic cells with pleomorphic vesicular nuclei with multiple mitotic figures (H&E stain, 40× magnification).

Discussion

Hypoglycemia that occurs with large nonpancreatic neoplasms of mesenchymal or epithelial origin is a well-documented entity in the medical literature. Approximately 200 cases of hypoglycemia associated with non-β cell tumors have been described since Doege and Potter first reported this entity in 1930 (1, 2). These tumors are usually very large in size; the largest tumor reported thus far was an abdominal spindle-cell sarcoma, weighing 9,000 grams (3), while the smallest one weighed 400 grams (4). Most tumors have exceeded 1,000 grams. Generally they are rather slow growing, with a low degree of malignancy, characterized only by local spread and al-

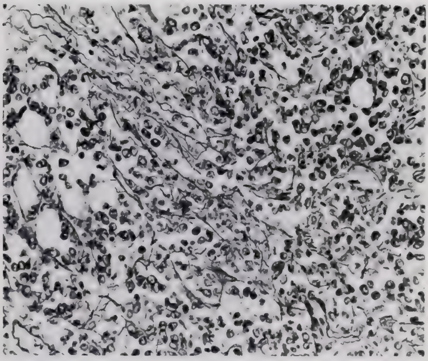

FIG. 4. Reticulin stain preparation of tumor specimen showing fine reticulin fibers surrounding tumor cell nests and individual tumor cells (40× magnification).

most equally distributed in the retroperitoneal (40%), intraperitoneal (32%), and thoracic cavities (28%). Unique are the very few cases that have been described of patients with preexisting diabetes mellitus in whom hypoglycemic inducing tumors subsequently developed (only four cases in a review series of 84 patients) (5). More than half of the tumors producing hypoglycemic episodes were of mesenchymal origin, the most common of which were large sarcomas (Table I). Malignant lymphomas associated with hypoglycemia have been reported, but these are much fewer in number. Furthermore, histiocytic lymphomas (reticulum-cell sarcomas) associated with hypoglycemia are extremely uncommon, with only a total of five cases reported in the literature (6–9).

TABLE I
Histologic Classification of Non-β Cell Tumors Associated with Hypoglycemia

1. Mesenchymal (64%)
   - Fibrosarcoma
   - Mesothelioma (benign, malignant)
   - Neurofibroma and neurofibrosarcoma
   - Spindle-cell sarcoma
   - Rhabdomyosarcoma
   - Leiomyosarcoma
   - Liposarcoma
   - Hemangiopericytoma
   - Hemangioendothelioma
   - Dermatofibrosarcoma protuberans
2. Epithelial
   - Hepatic (carcinoma, hepatoma) (21%)
   - Adrenal (carcinoma) (6%)
   - Others (9%)
     - Carcinoma of lungs
     - Hypernephroma and Wilm's tumor
     - Anaplastic carcinoma of stomach
     - Adenocarcinoma of cecum
     - Bile duct carcinoma
     - Cystadenocarcinoma and Dysgerminoma of ovary
     - Urinary bladder carcinoma
3. Miscellaneous
   - Chronic myelogenous leukemia and lymphomas
   - Pseudomyxoma peritonei
   - Paraganglioma

Pathogenesis of Hypoglycemia Associated with Non-β Cell Tumors

Many theories have been proposed to explain the possible mechanisms by which such tumors might produce hypoglycemia:

1. Nonhumoral mechanisms
   a. Excessive glucose consumption by the tumor
   b. The state of the liver: decrease in glucose output
   c. Late stage of terminal neoplasm
2. Humoral mechanisms
   a. Release of insulin or insulin like substances or insulin potentiator from the tumor
   b. Suppression of pancreatic glucagon secretion by the tumor

Nonhumoral Mechanisms

a. *Excessive glucose consumption by the tumor*

This theory has received considerable support in the literature. Adherents of this theory utilizing (C^{14}) glucose in their studies have proposed that some of these tumors may consume large quantities of glucose (10, 11). Thus, Bleicher and Chowdhury (12) found that tumor slices from a patient with a 2,300 gram mesothelioma utilized 5 mg of glucose per gram of tumor per hour or up to a total of 276 grams of glucose per 24 hours by the tumor alone.

b. *The state of the liver*

Decreased glucose output by the liver has been suggested as a possible mechanism in extrapancreatic tumor hypoglycemia. Both decreased glycogenolysis and gluconeogenesis with marked decrease in splanchnic glucose output were documented in a recent study of tumor-related hypoglycemia (13). Other factors considered include diminished glycogen stores in the liver secondary to hepatic metastases (14), decrease in lipolysis creating a lack of circulating free fatty acids and shift to increased glucose metabolism by the liver (15), as well as hypoglycemia secondary to chemotherapy-induced hepatotoxicity (16).

c. *Late stage of terminal neoplasm*

Hypoglycemia as a terminal manifestation of malignancy is quite common and can be the result of a variety of causes, such as severe malnutrition, malabsorption, and grossly impaired liver function (8).

Humoral Mechanisms

a. *Release of insulin or insulin like substances or insulin potentiator from the tumor*

A recent review of 120 cases of extrapancreatic tumors associated with hypoglycemia revealed that hypoglycemia could not be attributed to ectopic insulin production (17). However, insulin-like substances associated with tumor hypoglycemia have been identified. Thus, high levels of a nonsuppressible, insulin-like activity (NSILA) material, a composite of two insulin-like peptides referred to as insulin-like growth factors (IGF-1, IGF-2), were first discovered in the serum of about 50% of patients with non-β cell tumor hypoglycemia by Megyesi and her co-workers (9). It was noted that NSILA mimics insulin in both hypoglycemic and growth-stimulating effects. Also noted, in the same category as NSILA, is the nerve growth factor (NGF), which was first found to be produced by a huge liposarcoma of the buttock (18) and which was felt to be homologous to insulin (19). On the basis of the growth-stimulating effects of the above substances, it has been proposed that hypoglycemic tumors might produce excessive amounts of a growth factor with insulin-like activity. This too would be in keeping with the classically huge size of these tumors (17). Recently, high levels of another factor with insulin like activity, the insulin like protein (NSILP), was reportedly found to be associated with non-β cell tumor hypoglycemia (20). In addition to hypoglycemia, this factor was also found in conjunction with inhibition of lypolysis and impaired responsiveness to glucagon.

b. *Suppression of pancreatic glucagon secretion by the tumor*

Silbert et al (13) proposed the theory that an unknown factor secreted by the tumor, inhibiting pancreatic glucagon secretion, might be responsible for the non-β cell tumor hypoglycemia. In support of this, it was found that an extract from a mesenchymal tumor from a patient with severe hypoglycemia significantly suppressed the secretion of glucagon from the isolated perfused pancreas (21). The nature of such a presumed factor and its relationship to NSILP (also found to be associated with a decrease in glucagon secretion) (20) still remains unknown at the present time.

Conclusions

Hypoglycemia associated with nonpancreatic neoplasms and the theories suggested concerning its pathogenesis remain one of the most intriguing problems in medicine. The case presented in this paper has certain rare features in that severe hypoglycemia was found in a former insulin receiving diabetic, in whom the tumor was a huge histiocytic lymphoma of a very unusual type of non-β cell tumor associated with hypoglycemia. Although the serum NSILA was normal in this patient and the exact cause of hypoglycemia was not entirely clear, one could speculate that the hypoglycemia was probably mostly due to increased glucose consumption by the massive tumor. Additional possible explanations for the severe hypoglycemia might include malnutrition, malabsorption, or even the terminal stage of the lymphoma itself. Certainly other factors, as described previously, could be responsible for the patient's hypoglycemic status. In conclusion, we would like to suggest that the hypoglycemia as herein encountered might be of a slightly more common occurrence than currently realized and should, therefore, be sought in all patients with advanced lymphomatous disease.

Acknowledgments

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Angiographic Changes of the Canine Small Intestine Vasculature in Response to Acute Hemorrhage and Ligation of a Segmental Mesenteric Artery

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The effects of ischemia and hemorrhagic shock on the intestines have been studied in different species of animals (1–4). Alterations in intestinal blood flow and hemodynamics due to ischemia and shock have been documented in the dog (5). Changes of the microstructure of the enterocytes have been observed as early as three minutes following circulatory arrest in the dog's isolated small intestine (6). This report is a study of angiographic changes in the superior mesenteric artery (SMA) and its tributaries in the anesthetized dog in response to hemorrhage and intestinal segmental artery ligation.

Materials and Methods

Three groups of six mongrel dogs each weighing 15–25 kgs were studied. All experiments were carried out in animals anesthetized with a single intravenous injection of sodium pentobarbital (30 mg/kg). In each dog, a femoral artery was exposed and, under direct fluoroscopic control, a No. 7 end-hole French polyethelene catheter (I.D. 0.038 in) was threaded up the artery and aorta and into the ostium of the small mesenteric artery (SMA), where its tip was positioned securely. The test fluid used to visualize the vascular tree of the small intestine was diatrizoate meglumine and diatrizoate sodium 76% (renografin-76) with a viscosity of 9.1 cP. The contrast medium was administered by a cordis injector at a rate of 7 cc/sec over a period of three seconds. Exposure was set to visualize the arterial phase. Three different-sized arteries—the superior mesenteric artery, a mesenteric segmental artery (2°) and a tertiary artery (3°) (Fig. 1)—easily identified and well visualized, were selected in each of the dogs. Changes in the caliber of these arteries compared to the resting state (basal flow) in each of these arterial groups was studied.

In the first group studied, dogs were bled acutely to a moderate degree of hypovolemia by removing 25 cc/kg of whole blood from the contralateral artery over a period of five minutes. At the end of ten minutes the blood that had been withdrawn was retransfused. Injections of the contrast material into the SMA vasculature were repeated every two minutes throughout the procedure from time 0, (resting state).

In the second group of animals, the cecum, delivered from the abdominal cavity through a midline incision, was surrounded by saline soaked pads. The arterial supply as well as venous return of part of the cecal wall was occluded by ligation with a 2/o silk ligature. X-rays of the SMA vasculature were taken before ligating the cecal wall, 5 and 10 minutes immediately following ligation, and then every ten minutes for about an hour. The segmental 2° artery and the tertiary 3° artery chosen for observation were arteries of an adjacent ileal loop.

In the third group of dogs, after base-line SMA angiography, the arterial supply but not venous return of a 15 cm segment of ileum was occluded. SMA angiography was then repeated at two minute intervals for 14 minutes following the arterial occlusion.

Each animal served as its own control in determining the diametric changes observed in the

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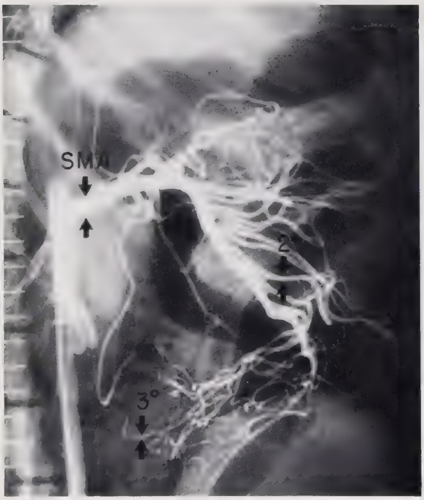

FIG. 1. Angiographic demonstration of the vasculature of the small bowel in the dog:—The superior mesenteric trunk (SMA), segmental artery (2), tertiary artery (3). The scale on the left border of the illustration is calibrated in centimeters.

three arterial groups studied under the different experimental conditions. Arterial measurements were performed with the aid of a pocket comparator 7× No. 183-901 Mitutoyo Optical Lens. Readings were done independently by three physicians not involved in the study.

Results

Acute hemorrhage in the Group I canines resulted in a 10% –20% reduction in diameter of the SMA vasculature (Fig. 2) Figure 3 illustrates the angiographic changes noted after cecal wall ligation in the Group II dogs. During the one-hour period of observation, no statistically significant alteration in diameter of the SMA and its branches were noted.

In the third group of animals (Fig. 4), a 40% vasodilatation of the tertiary (capillary) arteries was demonstrated. However, no statistically significant change in the caliber of the rest of the vasculature was noted.

Discussion

It has been generally accepted that injection of isotonic nonirritating fluids into an artery need not significantly alter hemodynamics in that vessel providing open communication is maintained between the distal portion of the vessel and the

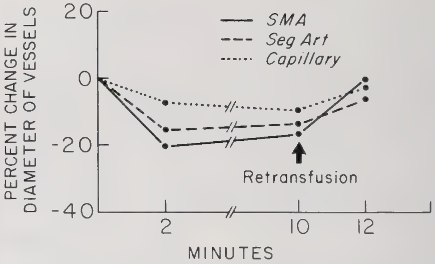

FIG. 2. Demonstrates changes in the diameter of the SMA, segmental artery and tertiary artery (capillary in the dog) in response to acute bleeding and re-transfusion of shed blood.

aortic lumen. However, recent studies (7, 8) have demonstrated increase in pressure and flow distal to the injection site during forced and/or rapid (7 cc/sec) arterial infusions. Moreover, alteration in blood pressure, heart rate, cardiac output, etc. are known to occur after the introduction of contrast media into the vascular system (9). The initial vascular response to a renografin 76 pulse has been described as being vasodilat (10). Since, in the present study, the same contrast medium, renografin 76, was injected through identical catheters at the same rate and pressure, the angiographic changes in the vasculature reflect hemodynamic alterations resulting from the experimental conditions.

In the first group of animals, acute moderate hypovolemia induced widespread angiographic vasoconstruction of the SMA and its branches. This effect probably reflects systemic hemodynamic changes. Gilmour et al (5) have shown that a decrease in cardiac output and venous central pressure occurred in the dogs even after minor

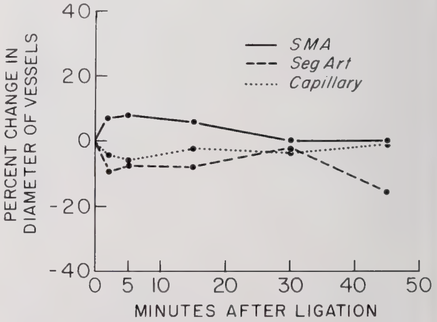

FIG. 3. Illustrates changes in the caliber of the vasculature of the small intestines in response to ligation of part of the cecal wall.

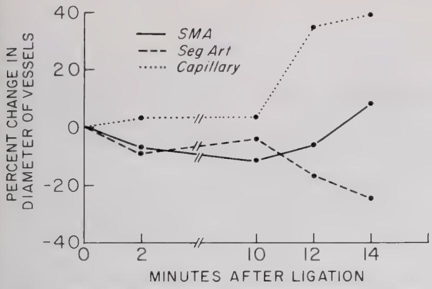

FIG. 4. Demonstrates marked vasodilation of the tertiary (capillary) arteries in response to segmental mesenteric arterial ligation.

(10%) bleeding. The neural-humoral reactions of the hypothalamic-adrenal axis that would follow the hemodynamic changes in response to hemorrhage can explain the vasoconstriction demonstrated angiographically in the SMA vasculature. Since all the intestinal vessels promptly resumed their basal diameters after restoration of blood volume, the relatively short period of hypovolemia, that is, ten minutes, probably precluded the release of vasoactive substances from the small intestines and, thus, obviated continuing hemodynamic phenomena.

In the second group of animals with ligation of the exteriorized cecal wall, no statistically significant changes in the diameter of the SMA vasculature were observed ($p > 0.25$). This result might have been anticipated since there was no hypovolemia, no absorption of bacteria and/or endotoxins from the ligated cecum, nor could any vasoactive peptide released from the ligated gut wall gain access into the portal circulation because of the venous occlusion.

In the third group of animals, the angiographic response to arterial ischemia of an ileal segment was a 40% increase in the diameter of the vessels distal to the arterial ligation. This phenomenon, commencing about ten minutes following ligature was statistically significant, $p < 0.01$. The remaining SMA vasculature showed changes which were not statistically significant, $p > 0.25$. It is probable that the marked vasodilatation observed resulted from the release from the ischemic bowel of vasoactive polypeptides (VIP). Initially, these polypeptides act locally and serve to improve perfusion. Later, entering the portal circulation, they manifest septemic effects, myocardial depression, decrease in C.V.P., lowering of the systolic pressure, etc. The study was concluded before these hemodynamic alterations could be observed.

Summary

1. Angiographic changes in the SMA vasculature in response to hypovolemia, arterial and venous occlusion, and small intestinal ischemia were studied in canines.
2. Prompt vasoconstriction of all SMA branches was demonstrated in response to acute moderate hemorrhage. This phenomenon was promptly reversed by blood volume restoration.
3. Cecal wall ligation induced no significant angiographic alterations under the experimental conditions.
4. Interruption of the arterial but not venous ileal blood flow resulted in marked vasodilation of the tertiary arteries distal to the arterial ligation suggesting release by the ischemic bowel of locally acting vasoactive polypeptides.

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Anesthetic Management of Cerebral Aneurysmectomy in a Sickle Cell Anemia Patient

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The recognition of sickle cell disease is of great importance prior to anesthesia because it influences the management of the patient throughout the perioperative period. Abnormal hemoglobins leading to sickling occur most commonly in those of African origin and in this condition hypoxemia or acidosis precipitates sickling and both may occur during anesthesia (1, 2). Sickling causes local stasis with hypoxia and acidosis with further sickling (3).

The common sickling conditions are:—sickle cell disease (hemoglobin SS), sickle cell trait (hemoglobin AS) and sickle cell B thalasemia (hemoglobin SBT). Since sickling depends on the amount of hemoglobins in the blood, the first two conditions are those which constitute the greatest anesthetic risk. We present a patient who underwent surgery for an intracranial aneurysm. The modification of our usual anesthetic management of this condition in a patient with sickle cell disease is discussed.

Case Report

A 23-year-old black woman was admitted for craniotomy and ligation of a right carotid-ophthalmic artery aneurysm. This had been diagnosed on cerebral angiography when she was admitted with severe neck pain. She had a history of sickle cell anemia, homozygous for hemoglobin S. A left interval carotid aneurysm had been clipped in this patient three years previously.

Her admission weight was 49 kgm. The blood pressure ranged from 110/70 to 125/80 Torr. The EKG, chest x-ray, serum electrolytes, and acid base status were all within normal limits. The hemoglobin level was 12.6 S following a transfusion of 1000 cc of fresh whole blood. The patient was hydrated by the intravenous route in addition to oral fluids preoperatively.

Premedication was with secobarbital 50 mg and atropine 0.4 mgs im one hour before operation. Prior to induction of anesthesia, a large peripheral venous catheter and a central venous catheter were inserted. The intrathoracic position of the latter was confirmed by chest x-ray. As the Allen test was equivocal in both right and left hands (possibly due to previous thrombotic episodes) a left dorsalis pedis arterial line was secured.

Following preoxygenation with 100% oxygen for five minutes, anesthesia was induced with sodium thiopental 250 mg iv and pancuronium 6 mg iv. The patient was ventilated with 0.5% halothane in oxygen and the larynx sprayed with 4 ml of 4% lidocaine. Endotracheal intubation was uneventful. Anesthesia was maintained with 0.5 to 2% halothane in oxygen. D-tubo-curare in a total dose of 60 mg iv was used to facilitate control of ventilation throughout the nine hour operation.

A moderate respiratory alkalosis, $PaCO_2$ between 25-35 Torr and pH above 7.45 was maintained and arterial PO_2 kept above 400 Torr. The patient was well hydrated with five liters of balanced salt solution. Urine output was three thousand milliliters. The patient's temperature was monitored with tympanic and oral probes. It was maintained at 36.5 to 37.7°C during surgery by a water warming blanket, warmed intravenous fluids, a semiclosed anesthesia circuit and an ambient temperature of 70°C. Mean systemic blood pressure was maintained in the range of 75–90 Torr.

At the end of the surgery, spontaneous respiration was reestablished after reversal with glycopyrrolate 0.8 mg iv and neostigmine 4 mg iv. Extubation was accomplished during 1% halothane anesthesia with oxygen to prevent straining on the endotracheal tube. Postoperatively the patient was maintained at an F_IO_2 of 0.5 for 24 hours. No sickle cell crisis or other untoward effect occurred postoperatively.

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Discussion

At this institution, standard management of patients for craniotomy includes:

1. Postoperative fluid restriction to reduce intracranial edema.
2. Premedication with atropine 0.4 mg im and secobarbital 100–150 mg im.
3. Peripheral and central venous lines.
4. A radial arterial line in the nondominant limb with 0.5% lidocaine anesthesia, providing Allen's test (4) is normal.
5. Standard EKG and blood pressure monitoring.
6. Anesthesia is induced with sodium thiopental 5 mg/kgm and pancuronium bromide 0.1 mg/kg. A 4% lidocaine spray to the larynx is followed by endotracheal intubation with blood pressure control. This is achieved by sodium nitroprusside (5–8) 10 mg/100 ml administered by a second anesthesiologist whose sole responsibility is to titrate the infusion against mean blood pressure.
7. Anesthesia is maintained with a neurolept technique of droperidol and fentanyl. Ventilation is with N_2O/O_2 in a 2/1 or 5/2 ratio. The mean arterial pressure is kept at 70 Torr while the cranium is opened and during clipping of the aneurysm if there is no cardiovascular, hepatic or renal disease which would contraindicate this.
8. At the conclusion of surgery, muscular relaxation is reversed by a glycopyrrolate-neostigmine combination, the patient is awakened and the endotracheal tube removed while the patient is on the operating table to avoid coughing or bucking on the tube.

Modification of this management in patients with sickle cell disease included adequate hydration with both oral and intravenous fluids since these patients are prone to dehydration. Repeated hemoglobin estimations were made to ensure an adequate level. Folic acid was given orally to prevent marrow output failure and a vigorous search made for infection, especially pulmonary which is associated with nine high incidences of postoperative pulmonary thrombosis and pneumonia. Sulfa containing drugs are avoided as they may precipitate a hemolytic reaction if the patient has a glucose phosphate dehydrogenase deficiency.

Searle (6) recommends preoperative transfusion if the hemoglobin level is below 5 G/100 ml, while Howels et al (3) transfuse their patients if the hemoglobin is below 7 G/100 ml. The two units of blood given to our patient ensured a level of 12.4 G/100 ml. We took an arterial blood sample preoperatively and as no acidosis was present in this patient alkalinization was unnecessary (7, 8, 9, 10, 11).

Premedication is kept to a minimum to avoid respiratory depression.

During induction and maintenance, efforts were directed at avoiding hypoxia or hypotension so sodium nitroprusside was not used. We felt this would increase the risk of acidosis and hypotension and so increase intrapulmonary shunting with a lowering of PaO_2. Preoxygenation for five minutes ensured a high PaO_2 in our patient. Blood pressure control was achieved by ventilation with a halothane/oxygen combination.

Anesthetic maintenance was with halothane 0.5%–2% in oxygen as used by Homi et al (8). A volatile agent (3–8) has been recommended as minimizing hypocapnic vasoconstriction thus providing good tissue perfusion. Circulatory stasis was avoided by generous intravenous fluid with central venous pressure control. This also lowered blood viscosity and the chance of crisis. Usually fluid is restricted to two liters of crystalloid.

Repeated arterial blood gas estimations were made. This enabled us to maintain a high PaO_2 and $PaCO_2$ 25–35 Torr. The slight respiratory alkalosis counteracts a tendency to acidosis but avoids hypocapnic vasoconstriction.

A heating blanket was used to avoid cooling.

Although blood replacement was not necessary, fresh blood with its high 23 D.P.G. content was always available.

To avoid hypoxia at extubation; the muscle relaxant was reversed early and $PaCO_2$ levels allowed to rise slowly while anesthesia was maintained with the halothane/oxygen mixture to permit smooth removal of the endotracheal tube.

The patient received supplemental oxygen (12, 13) for 36 hours postoperatively at an F_IO_2 of 0.3-0.5. Hydration was continued, prophylactic antibiotics were not given and postoperatively early mobilization started.

Searle has recommended that the most important aspect of sickle cell disease management are its detection preoperatively and the attention to detail in conduct of anesthesia. This latter factor is of greater importance than the choice of anesthetic agent (6). There is no evidence that uneventful anesthesia can trigger serious manifestations of sickle cell disease. Some studies have actually shown a decrease in sickle cells during anesthesia and for some time postoperatively (7, 10).

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Polyneuropathy, Papilledema, and Plasmacytoma

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Abstract

A 28-year-old woman with a subacute progressive sensorimotor polyneuropathy was found to have a solitary plasmacytoma. Later, she developed bilateral papilledema without evidence of intracranial mass lesion. An IgG lambda spike was found on serum immunoelectrophoresis. The patient was treated with localized radiation to the tumor and later with chemotherapy. Objective clinical improvement of the polyneuropathy began three months after the start of chemotherapy and five months after completion of irradiation to the plasmacytoma. It is essential to do a skeletal bone survey and serum immunoelectrophoresis in all adult patients with a subacute or chronic polyneuropathy.

Polyneuropathy in patients with multiple myeloma is uncommon. It is even less frequent in patients with a solitary plasmacytoma of bone. Also quite rare is papilledema in patients with polyneuropathy without any evidence of intracranial mass lesion. This report concerns a unique case of a progressive subacute polyneuropathy, papilledema, and a solitary plasmacytoma of bone.

Case Report

A 28-year-old white female acrobatic dancer was evaluated at another hospital in August, 1978 with a four-month history of progressive weakness and numbness of the lower limbs. Three weeks after an upper respiratory infection in March, 1978, the patient started noticing leg weakness which caused difficulty in dancing and running. There was a pressure sensation in the calves, and the toes were occasionally numb. For one month, she had noticed daily swelling of both feet and ankles. There were no bulbar or visual complaints, no sphincter difficulties and no headaches. She had not been exposed to heavy metals or other neurotoxic substances, and family history was negative for neuromuscular disease. Initial neurologic exam revealed normal cranial nerves including funduscopy, mild proximal leg weakness, decreased vibration of both feet, and absent deep tendon reflexes. The following lab tests were nomal: CBC, CPK, sedimentation rate, VDRL, thyroid functions, ANA and LE preparation. Lumbar puncture revealed an opening pressure of 190 mm Hg with a spinal fluid protein of 237 mg% and no cells. X-rays of the chest, thoracic and lumbosacral spine were reported as normal. The patient was discharged on a two-week course of prednisone 40 mg daily.

Because of increasing distal leg weakness, the patient was readmitted in November, 1978. A complete myelogram was normal, with the cerebrospinal fluid showing no cells and a protein of 238 mg%. Lumbosacral spine x-rays now revealed a well demarcated lytic bone lesion in the left acetabular region. It was believed that the bony changes were indicative of a benign lesion, and a differential diagnosis of giant cell tumor, aneurysmal bone cyst, and fibrous dysplasia was suggested. A bone scan showed increased activity over the left acetabulum, and an intravenous pyelogram was normal. The patient was discharged without improvement.

Electrodiagnostic studies in November, 1978 showed extensive distal denervation changes with slow motor and sensory nerve conduction velocities in all limbs. By New Year's Day, 1979,

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the patient was now complaining of some numbness in both hands and a constant pulling sensation in her feet at night. She now had poor hand and finger coordination and difficulty writing. Examination at this time revealed the following findings: severe bilateral foot drop with wasting of the calves and inability to move the toes or feet at all, moderate weakness of the proximal leg muscles, normal strength in the arms and hands, bilateral areflexia with absent plantar responses, loss of vibratory and position sensation over both feet with a milder loss over the fingers, and intact pain, temperature, and light touch sensation.

Because of the continued progression of the distal sensorimotor polyneuropathy, a course of prednisone 100 mg on alternate days was begun in January, 1979 (nine months after the initial symptoms). There was only minimal improvement in foot strength, and, four months later, tapering of steroids was initiated. On routine neurologic exam of July 21, 1979, the patient was found to have bilateral papilledema, and was admitted to The Mount Sinai Hospital. The patient had no complaints of headache, nausea, vomiting, or visual disturbance. She described a four-month history of mild left hip pain on weight bearing.

General physical examination was normal except for 2+ pitting edema of the feet and ankles. Mental status was normal. Bilateral papilledema was present on funduscopic examination. Visual acuity was normal and visual field testing revealed enlarged blind spots. There was mild distal weakness in the arms and severe distal weakness with atrophy in the legs. There was a prominent steppage gait. Sensory examination showed markedly decreased vibratory sensation up to the hips with mild loss in the fingers, decreased position sensation in both toes and ankles, and decreased pin and thermal sensation below both knees. Deep tendon reflexes were absent throughout, and the plantar reflexes were unelicitable.

A CT scan of the brain was normal. Lumbar puncture showed an opening pressure of 210 mm Hg; the fluid was acellular with a protein of 122 mg%. The prednisone dosage was gradually discontinued. X-rays of the pelvis showed considerable growth of the lytic lesion in the left acetabulum (Fig. 1). The following blood tests were normal: CBC, calcium, alkaline phosphatase, fasting glucose ×3, creatinine, protein, albumin and sed rate. Cellulose acetate serum protein electrophoresis showed a homogeneous spike in the gamma globulin range (Fig. 2), and on agarose gel immunoelectrophoresis the spike was identified as a monoclonal IgG lambda paraprotein (Fig. 3). Quantitative immunoglobulin levels (in mg %) were IgG = 1390 (nl 800–1500), IgA = 98 (nl 120 − 380), and IgM = 150 (nl 40 − 160). The urine was negative for Bence-Jones protein. Open biopsy of the left pelvic lesion revealed plasmacytoma. Bone marrow aspiration of the left iliac crest was normal, with 3% normal plasmacytes. Complete metastatic skeletal survey failed to reveal any further bone lesions. Muscle biopsy of the left quadriceps was mildly abnormal as noted by small angulated fibers consistent with early denervation. The left pelvic lesion was irradiated locally with a cumulative tumor dose of 5500 rads over a four week period. Six weeks following completion of radiation therapy the patient was re-admitted for curettage of the left hip lesion and bone graft. Open curettage of the lesion disclosed plasmacytoma still present. Repeat serum protein electrophoresis and immunoelectrophoresis showed a persistent IgG lambda spike with no change in quantitative immunoglobulin levels. Clinically, the patient was unchanged.

Two months following completion of radiation

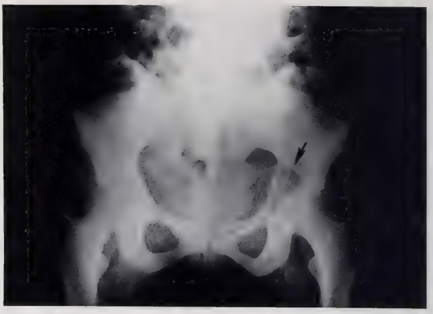

FIG. 1. X-ray of pelvis. There is a lytic lesion in the left acetabulum (arrow).

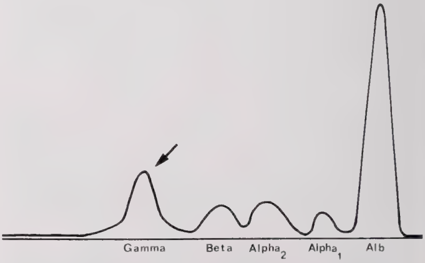

FIG. 2. Serum protein electrophoresis. Arrow indicates homogeneous spike in gamma globulin range. Alb. = Albumin.

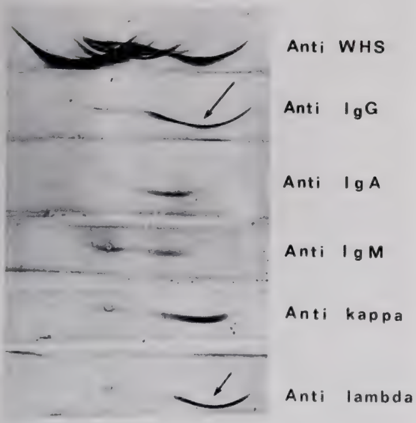

FIG. 3. Immunoelectrophoresis of serum. Arrows indicate IgG lambda paraprotein component. WHS = Whole Human Serum.

therapy, the patient was established on a seven-day course of melphalan (10 mg/day) which was repeated six weeks later. Six weeks after this course, she was switched to maintenance melphalan (2 mg/day) and prednisone (20 mg/day). Five months after radiation therapy and three months after the start of chemotherapy, objective clinical improvement was first noted in that she showed movement in the foot flexors and extensors, muscles which previously had shown virtually no movement at all. This improvement continued so that five months postchemotherapy, the patient could balance herself on one leg without holding on, drive a car, sew, and button her shirt normally—all functions she previously could not perform. Vibration and position sensation in the toes, previously absent, improved in that she could feel vibration in both toes, and position sense in the right big toe. The papilledema also subsided.

Discussion

Sensorimotor polyneuropathy is an uncommon finding in patients with multiple myeloma (MM). Silverstein and Doniger (1) were able to find only nine patients (3%) with chronic polyneuropathy in a series of 277 cases of myelomatosis. Polyneuropathy associated with solitary plasmacytoma of bone (SPB) is even less common. Read and Warlow (2) could document only 16 "acceptable cases" in the literature (including their three cases).

The clinical presentation of the polyneuropathy of SPB and MM is indistinguishable from that of most other subacute or chronic polyneuropathies. It consists of a progressive, symmetrical weakness of the distal muscles of the extremities, the legs being affected first and to a greater degree than the arms. The symmetrical sensory loss, also more prominent distally and in the legs, may involve all of the primary sensory modalities. Areflexia is present early, and as the disease progresses, atrophy of the distal musculature becomes apparent. Limb pains and pedal edema may occur. Cranial nerve and respiratory muscle involvement is uncommon.

Distinguishing characteristics of patients with SPB and polyneuropathy include (2): symmetrical, progressive sensorimotor polyneuropathy as an initial presenting complaint rather than bone pain or another myeloma complication, elevated CSF protein, normal bone marrow, no Bence-Jones proteinuria and normal ESR. Our patient is more atypical in both her age and sex characteristics. The MM patient with polyneuropathy is commonly diagnosed ten years younger than the average myeloma patient (3). This is ascribed to an earlier complete medical workup for a seemingly unrelated polyneuropathy. In Read and Warlow's series (2), the mean age of presentation was 49, with the youngest patient 34. Our patient developed her first symptoms of polyneuropathy at age 27, and is therefore the youngest reported case. In the same series, 15 of 16 cases were male; their one female case was felt to be "atypical" in that she had a mostly sensory polyneuropathy and had progressive worsening of MM. Our patient is female, and is certainly not atypical in her clinical or laboratory presentation.

Our patient's bone lesion was in the left pelvis. The most common sites for SPB are the ribs, spine, and bones of the pelvic and shoulder girdles (4, 5). In Read and Warlow's series (2) only two of 16 cases had a pelvic lesion. The tumor is typically a large well demarcated lesion with bubble like lytic areas. Such a tumor is often mistaken by the radiologist as a benign giant cell tumor of bone (4). An osteosclerotic bone lesion, felt to be more common in myeloma patients with polyneuropathy, was not seen in our case (6).

A low electrophoretic spike in the gamma globulin fraction as in this case is not unusual in localized plasma-cell tumors (7). This emphasizes the importance of performing the more sensitive serum immunoelectrophoresis, which uses polyvalent and monospecific antiserum for various heavy and light chains (8, 9). According to Woodruff (5) the detection of a serum paraprotein in a patient with a histologically proven solitary plasma cell tumor and normal bone marrow does not exclude the diagnosis of SPB. Patients with SPB have anywhere from a 16% to 65% incidence of abnormal serum paraproteins (4–7). On the other hand, Bergsagel (8) and Kyle (9) are skeptical about a description of solitary plasmacytoma with a myeloma paraprotein spike as a distinct entity from MM. In Read and Warlow's series of SPB with polyneuropathy (2), only two of 15 recorded cases had abnormal serum paraproteins.

The pathologic findings in the peripheral nervous system are similar in patients with SPB and MM, and also in those with uremia, diabetes mellitus and carcinoma. They include segmental demyelination of peripheral nerves with variable amounts of axonal loss, the process sometimes extending to nerve trunks and roots (3, 10, 12). The etiology of the neuropathy associated with plasma cell tumors is unknown. Disseminated amyloidosis has been reported as occuring in 15% of patients found at autopsy to have plasma cell tumors. However, actual pathologic confirmation of amyloid deposits in the small vessels of peripheral nerves is quite rare, having been found in only five reported cases of myeloma polyneuropathy (10, 11, 14, 15). Direct infiltration of nerves with myeloma cells has also been reported (16). The vast majority of cases with myeloma polyneuropathy have revealed neither amyloid nor myeloma cell infiltrates. Other possibilities of damage to peripheral nerve include toxins or antibodies produced by the tumor against nerve or myelin, hyperviscosity secondary to hyperproteinemia with subsequent nerve ischemia; generalized vasculitis causing vascular insufficiency; and relative deficiency of essential nerve metabolites due to competitive utilization by the tumor. None of these hypotheses has ever been substantiated.

Myeloma polyneuropathy associated with papilledema was once thought to be quite rare, having been reported in only two cases prior to 1968 (17, 18). Since that time, several reports from Japan have described a syndrome of plasma cell dyscrasia, polyneuropathy, and endocrine disturbances (19–21). In the largest series of this syndrome (32 patients), all patients had a progressive sensorimotor peripheral polyneuropathy (20). Most had relatively small M protein spikes in the serum (either IgG or IgA heavy chains with lambda light chains) and many were associated with osteosclerotic bone lesions, either solitary or multiple. In addition, the patients had varying amounts of endocrine, cutaneous, and visceral disturbances. These disturbances included the following: diabetes mellitus or impaired glucose tolerance, gynecomastia and impotence in males, amenorrhea in females, pedal edema, ascites and pleural effusion, hypertrichosis, finger clubbing, white nails, skin hyperpigmentation, and hepatosplenomegaly. Nineteen of twenty-five cases examined had papilledema, and all had elevated spinal fluid protein. Many of these patients received various combinations of radiation therapy, alkylating agents and steroids, though it is not specified which patients with papilledema received steroids. The underlying mechanism responsible for this combination of symptoms is unclear, but it is felt by the Japanese authors that some biologically active factor other than the M protein is produced by the abnormal plasma cells. Our patient lacked most of the associated findings of this syndrome, except for the pitting pedal edema and white toe nails.

Papilledema in our patient was first noted some 16 months after the beginning of symptoms of a polyneuropathy, several previous funduscopic exams having been normal. The association of papilledema with other polyneuropathies is also uncommon. Most reported cases associate papilledema with the acute idiopathic type of polyneuropathy, so-called Guillain-Barré Syndrome (22–27). Clinical features and CSF findings in these cases are similar to those in uncomplicated Guillain-Barré patients except for a slower progression of the illness, an increase in cranial nerve involvement, and an increased incidence of relapsing cases (26). There is a clear correlation between the development of papilledema and an increase in CSF pressure. In one study (26) 19 of 23 cases measured had CSF pressure greater than 200 mg Hg. In this study, a less definite relationship was found between papilledema and the level of elevated CSF protein—almost half the cases had a protein less than 40 mg%. The occurrence of papilledema has also been noted in 7% of patients with chronic inflammatory polyneuropathy (28, 29).

Papilledema when found in cases of myelomatosis has almost always been due to myelomatous deposits in the skull with resulting brain compression and increased intracranial pressure (1). Intracranial plasma cell tumors have also been reported (30, 31). Theories as to the pathogenesis of papilledema in the Guillain-Barré

Syndrome, which could also apply to that of myeloma polyneuropathy, are (i) protein occludes the arachnoid villi causing decreased CSF absorption and resultant increased intracranial pressure (23); (ii) the polyradiculoneuropathy itself caused diffuse cerebral edema (25) and; (iii) increased protein raises the osmotic pressure of the CSF and hence causes increased CSF volume (26).

In this case, another possible cause was that papilledema occurred during a prolonged course of steroid reduction. The association of papilledema with reduction of steroid therapy has been reported exclusively in the pediatric population by several authors (32–36). The children, ranging from 2 to 19 years of age, had been taking chronic oral steroids for various diseases, including asthma, nephrotic syndrome, and ulcerative colitis. In the typical case, a child's steroid therapy was either tapered in dosage or changed to a different steroid. Greer (33) proposes that the cause of the syndrome is a transient adrenal insufficiency resulting in cerebral edema, while Johnston, et al (37), in a study on the effects of steroid withdrawal in dogs, found a marked reduction in CSF absorption.

The preferred treatment for myeloma polyneuropathy, particularly the type associated with SPB, is local radiation to the tumor site. Reviews of the topic have pointed out a striking difference in those patients receiving local radiation as compared with those who received either no therapy or just chemotherapy (2, 38). The patients with radiation almost always showed subsequent improvement of the polyneuropathy. The nonradiated patients generally showed no improvement.

The present case further confirms that the neuropathy of myeloma is one of the few treatable chronic neuropathies. After two years of a progressive sensorimotor polyneuropathy, objective clinical improvement began three months after the start of chemotherapy for myeolma and five months after completion of localized irradiation of the SPB. She is also the youngest reported case of polyneuropathy associated with solitary plasmacytoma of bone. Furthermore, this case emphasizes the importance of performing a serum immunoelectrophoresis and skeletal bone survey in any adult patient with subacute or chronic polyneuropathy. These studies are necessary if a plasma cell dyscrasia is to be discovered and treated.

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Idiopathic Hypertrophic Osteoarthropathy without Pachyderma and with Acrolysis

Sergio Schwartzman, B.A. and Harry Spiera, M.D.

Idiopathic hypertrophic osteoarthropathy (also known as pachydermoperiostosis) is a syndrome characterized by clubbing of the digits, periosteal new bone formation and thickening of the skin. In extremely rare instances, idiopathic hypertrophic osteoarthropathy (IHOA) may present without skin lesions. In addition, two cases of IHOA have been reported in which extensive acrolysis was present. However there have been no reports describing both conditions in the same individual. In this report we describe a case of IHOA in which acrolysis was present and skin lesions were absent.

Case Report

The patient is a 22-year-old oriental male who presented with clubbing and painful knees and ankles.

The patient had first noted clubbing of the digits of the upper extremities in childhood and progressive enlargement of both his knees and ankles since late adolescence. Over the last few months, the knee and ankle joints had become painful on movement. He denied any skin changes or hyperhidrosis. There was no family history of clubbing. The patient had been born prematurely and required hospitalization after birth. In addition, at one time during childhood, the patient received growth hormone for an unknown reason. There was no history of cardiac, pulmonary, gastrointestinal or endocrine disease.

Physical examination revealed a well developed male with marked clubbing of both upper and lower extremities. The knee and ankle joints were enlarged bilaterally and there was pain on movement. The patient did not have pachyderma or any other skin changes.

Roentgen examination on presentation revealed periosteal new bone formation in the diaphyses of the tibiae and fibulae (Fig. 1). Roentgenograms of the hands and feet (Figs. 2, 3) revealed atrophic changes of varying degrees limited to the terminal phalanges. The extent of resorption varied from thinning of the shafts to extensive acrolysis. Chest roentgenogram was normal as were routine blood chemistries, sedimentation rate and CBC.

Discussion

IHOA is a syndrome characterized by clubbing of the digits, periosteal new bone formation especially over the distal ends of the long bones, and thickening of the skin with coarsening of the facial features (1). In addition, this disorder is frequently associated with hyperhidrosis of the palms and soles, painful joints and cutis verticis gyrata (2). The syndrome starts usually during adolescence, runs a progressive course for several years and is self limited, being compatible with a normal life span (2, 3). Although it has been described predominantly in males, this disorder may appear in both sexes (4). A familial incidence has been well established with an incompletely penetrant dominant gene being responsible for transmission (3, 4).

Roentgenographic findings in IHOA (3, 5, 6) are characterized by an irregular subperiosteal ossification over the distal ends of the long bones. Similar findings may be present in the metacarpal and metatarsal bones and the proximal phalanges. The terminal phalanges are usually uninvolved although burr formation and nonspecific atrophic changes may be present.

A second more common form of osteoar-

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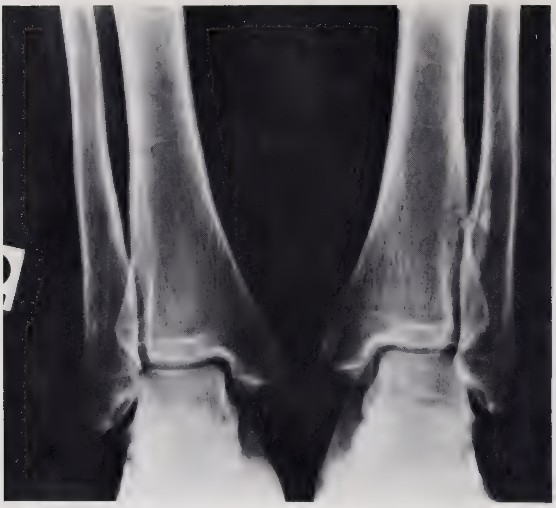

FIG. 1. Periosteal new bone formation in the diaphyses of the tibiae and fibulae.

thropathy known as secondary hypertrophic osteoarthropathy or pulmonary hypertrophic osteoarthropathy occurs most often in the presence of a pulmonary tumor or abscess; although, chronic cardiac, hepatic, gastrointestinal, or endocrine disease may also predispose to the development of this condition (2, 7). All clinical aspects of IHOA may be seen in the secondary form and it is now well established that differentiation of the two forms must be based on the presence or absence of a primary lesion, a family history and the clinical course (3, 4).

In the original paper separating IHOA from pulmonary hypertrophic osteoarthropathy (1), Touraine, Solente and Gole subdivided IHOA into three classes: The complete form with pachyderma and pachyperiostosis; the incomplete form without involvement of the scalp; and a form

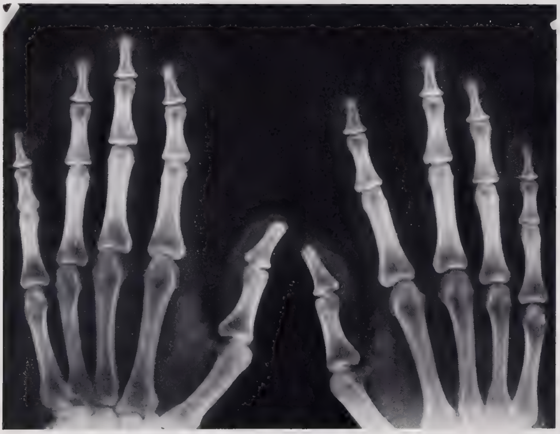

FIG. 2. Roentgenogram of the hands demonstrating atrophic changes in the terminal phalanges and clubbing.

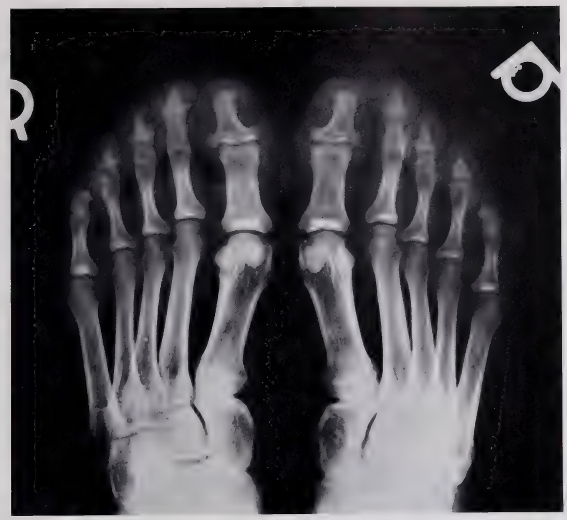

FIG. 3. Roentgenogram of the feet demonstrating extensive resorption of the terminal phalanges and clubbing.

fruste with clubbing and thickening of the skin but without periosteal changes. More recently, other variants have been described. Among these, several cases of IHOA without pachyderma have been reported (2, 6, 8–11) and two cases of extensive distal phalangeal resorption have been described (12, 13). Our case is unique for presenting with both of these unusual features in a single individual.

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Bronchogenic Carcinoma With Symptomatic Metastasis to the Stomach: A Case Report

Suresh Tawney, M.D., Herbert W. Berger, M.D., Damasus S. Jayamanne, M.D., and Manoon Lee, M.D.

Abstract

We report the fourth case in the medical literature of symptomatic gastric metastasis from carcinoma of the lung. This metastatic lesion was seen as an ulcerating mass on upper gastrointestinal series and the diagnosis was confirmed by gastroscopic biopsy. Both the biopsy of the primary tumor in the left lower lobe and the gastric metastasis showed poorly differentiated epidermoid carcinoma.

Symptomatic gastric metastases from carcinoma of the lung are extremely rare. The first recorded case of clinically significant metastatic disease from bronchogenic carcinoma to the stomach appeared 19 years ago, and only three other cases have been reported since (1–3). We report a fourth patient with this unusual metastatic site of primary lung cancer.

Case Report

A 65-year-old man was referred to Mount Sinai Services-City Hospital Center at Elmhurst, New York, in September 1980 with a three-to-four year history of epigastric pain partially relieved with antacids, nausea, vomiting, anorexia, and weight loss of one month's duration, and an abnormal chest roentgenogram. He denied dysphagia, hematemesis, or melena. He also gave a history of increasing productive cough for one month and one episode of hemoptysis 20 days prior to admission. The patient had a smoking history of 1–2 packs of cigarettes per day for 35 years.

Physical examination revealed normal vital signs. Examination of the chest was unremarkable. There was no clubbing, lymphadenopathy, abdominal tenderness, or organomegaly. A complete blood count, SMA-6, and SMA-12 were within normal limits. The stool guaiac test was negative. The chest roentgenogram (Fig. 1) showed a mass 5 cm in diameter with ill-defined margins in the superior segment of the left lower lobe.

Bronchoscopy revealed a whitish mass 2 × 2 cm in the superior segment of the left lower lobe. Biopsy showed poorly differentiated epidermoid carcinoma.

An upper gastrointestinal series (Fig. 2) revealed an ulcer on the lesser curvature of the stomach, and a moderate-sized ulcerated mass and irregularities of the greater curvature. Gastroscopy demonstrated a circumferential ulcerating mass involving the greater curvature and posterior wall of the lesser curvature. Biopsy showed poorly differentiated epidermoid carcinoma identical with the bronchial biopsy.

The patient was treated with chemotherapy with no immediate improvement.

Discussion

Although carcinoma of the lung metastasizes widely, spread to the gastrointestinal tract is uncommon. The incidence of gastrointestinal metastasis in an autopsy series of 3,047 cases of bronchogenic carcinoma collected by Oshsner and DeBakey (4) was 4.3 percent.

Clinically apparent gastric metastases from primary carcinoma of the lung are rare, with only three cases previously reported (1–3). In these three cases, the primary tumor was in the right upper lobe while, in our patient, it was in the left

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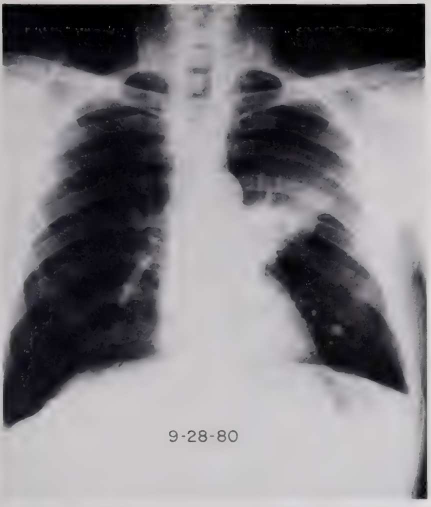

Fig. 1. Chest x-ray showing mass in left lower lobe.

lower lobe. In two previous patients, the tumor histology was squamous cell carcinoma as in our patient, while the third patient had undifferentiated carcinoma (Table I).

Tumors which most commonly metastasize to the stomach are malignant melanoma, carcinoma of the breast, and carcinoma of the lung (5).

Initial seeding in hematogenous spread to the stomach occurs in the submucosa irrespective of the primary tumor (1, 5). As the lesions enlarge they form atypical submucosal masses or, less commonly, extend as circumscribed submucosal plaques which often extend into the mucosa and later ulcerate.

Simao (2) reported a patient with gastric metastasis from bronchogenic carcinoma whose upper gastrointestinal series showed a "bull's-eye" lesion, such as previously had been described only in metastatic malignant melanoma of the stomach.

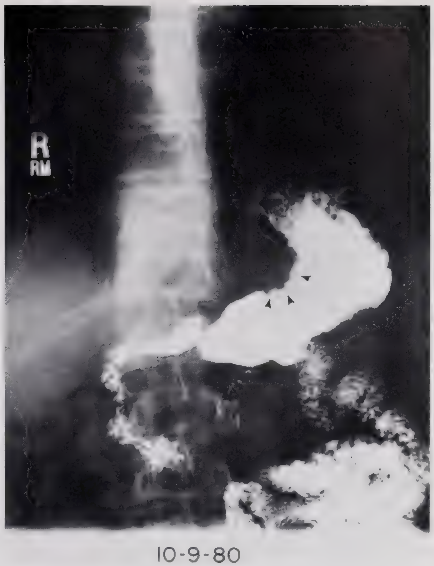

Fig. 2. Upper gastrointestinal series showing ulcerated mass in stomach.

Carcinoma of the stomach frequently produces lymphangitic metastases to the lungs and pleural effusions but does not produce single or multiple nodules greater than a few millimeters in diameter.

Radiation of metastatic lesions from bronchogenic carcinoma might predispose patients to increased risk of gastric perforation. This would be comparable to cases of small bowel metastases from bronchogenic carcinoma which perforated following extensive radiation treatment (6, 7).

A patient with radiographic and endoscopic evidence of tumors in both the lung and stomach

TABLE I

Characteristics of Gastric Metastases from Bronchogenic Carcinoma

Date	Author	Stomach Gross Pathology	Bronchogenic Carcinoma Site	Pathology
1962	Higgins et al[1]	Spherical mass in pylorus	RUL	Undifferentiated carcinoma
1963	Simao et al[2]	Ulcerated mass in wall of stomach	RUL	Squamous cell carcinoma
1974	Morton et al[3]	Ulcerated mass on greater curvature	RUL	Squamous cell carcinoma
1981	Tawney et al	Circumferential ulcerated lesion on greater and lesser curvature	LLL	Squamous cell carcinoma

most commonly has two independent primary carcinomas with different histologic characteristics. Rarely however, as in this report, bronchogenic carcinoma may produce symptomatic metastases in the stomach. The fact that tumor histology is identical in both patients and is undifferentiated epidermoid carcinoma confirms this supposition.

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Metachronus Carcinoma of the Colon 25 Years After Resection of Colonic Pulmonary Metastases

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Abstract

A 79-year-old female underwent a diverting colostomy for an obstructing colon malignancy 31 years after resection of a carcinoma of the rectosigmoid colon and 25 years after resection for pulmonary metastases. Patient surviving colon cancer with or without treatment for metastatic disease must be watched carefully for the occurrence of a metachronus colon carcinoma. The case described illustrates this point.

The results of resection of solitary pulmonary metastases are similar to resection of primary lung cancers (1). The patients who survive must be followed not only for recurrence of their colon cancer, but also for the appearance of a metachronous colon malignancy. We present such a case, first reported in this journal in 1961 (2).

Case Report

G.A., at age 52, underwent an abdominoperineal resection in 1948 for a carcinoma of the rectum, pathologically reported as "polypoid adenocarcinoma of colon with early infiltration. No involved lymph nodes found." The patient was asymptomatic until 1955 when minimal hemoptysis prompted a chest x-ray which revealed a fusiform shadow in the anterior basal segment of the right lower lobe of the lung. Evaluation resulted in a clinical diagnosis of primary peripheral lung cancer. Resection was performed (P.A.K.) of the right lower and middle lobes for what appeared to be a primary carcinoma. The microscopic pathologic report was "multiple adenocarcinomata (one large and two small), probably metastatic. No involved lymph nodes found." The tissue was identical to the prior colon lesion.

The patient did well and was disease free five years after the lung resection. Eventually, she was lost to follow-up. She remained in remarkable good health until August 1979, when she noted decreased function of her colostomy associated with progressive abdominal distention. On August 20, 1979, she was admitted to Long Beach Memorial Hospital with marked abdominal distention and constipation of five days duration. Physical examination revealed an acutely ill 83-year-old female with a distended, tympanic abdomen and no stool in the colostomy. An emergency barium enema disclosed complete obstruction to retrograde flow in the distal transverse colon consistent with a malignant lesion (Fig. 1). A chest x-ray was compatible with multiple pulmonary metastases (Fig. 2). An emergency loop transverse colostomy was performed. At laparotomy, a typical annular carcinoma of the distal transverse colon was identified. The patient had an uneventful postoperative course, but had to be re-admitted four weeks postcolostomy for treatment of deep vein thrombophlebitis of the right calf. Conservative measures eventuated in resolution of the acute symptoms. The patient's condition deteriorated with progression of the pulmonary metastases and she expired four months after the last surgical procedure.

Discussion

Since Divis' (3) reported resection of a solitary pulmonary metastasis in 1927, gratifying results have been obtained with this procedure. Resection of solitary colonic metastases have given particularly excellent long-term benefits (4). The patients who do survive five years, approximately

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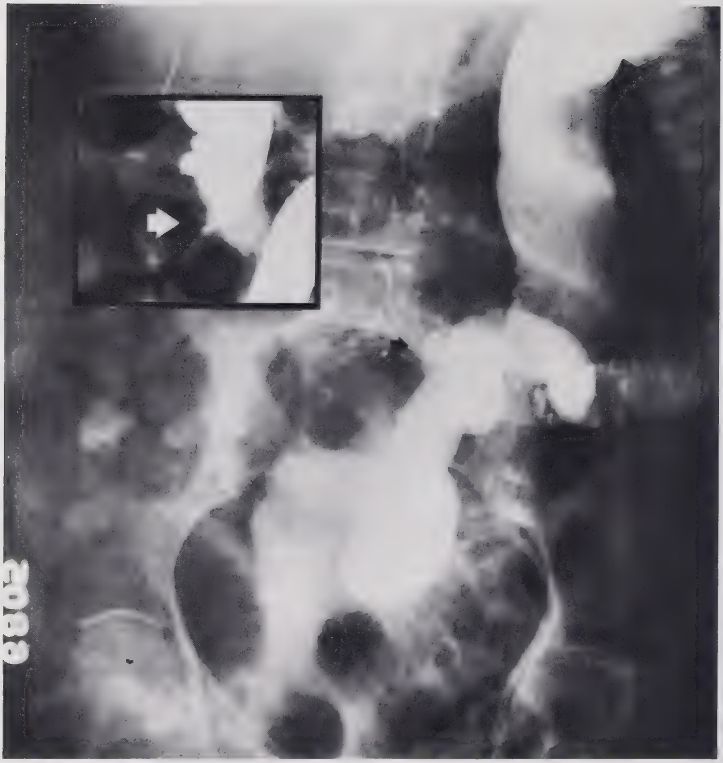

FIG. 1. Barium enema demonstrating an obstructive lesion of the transverse colon.

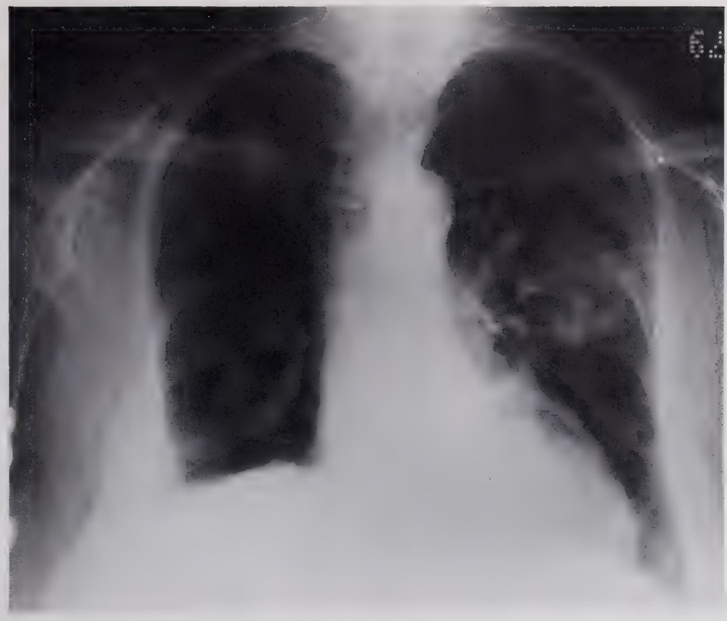

FIG. 2. Chest X-ray demonstrating multiple pulmonary metastasis.

30 percent, are at the same risk of developing a metachronous colon carcinoma as those who did not have lung metastases. Therefore, all these patients must be followed with guaiac stool testing, sigmoidoscopy, barium enemas and colonoscopy as indicated. The case reported represents the success of surgical therapy and failure of follow-up, with loss of the patient from a metachronous colon carcinoma recognized only after the disease had widely disseminated.

Bussey et al (5) addressed the probelm of metachronous carcinomas of the colon in their report on 3381 patients who survived conventional resection of the colon and rectal cancers. An overall incidence of approximately three percent was noted for metachronous carcinomas in patients followed at least 20 years. These findings stress the need to keep those patients undergoing colon resection with or without resection of pulmonary metastases under supervision perennially. This would allow recognition of a second colon cancer while it was still localized and therefore curable.

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Neurologic-Neurosurgical Notes

Allen E. Rubenstein, M.D. and Martin H. Savitz, M.D., Coeditors

Fibrosarcoma of the Spinal Meninges in a Case of Neurofibromatosis

MARTIN H. SAVITZ, M.D., STUART D. LESTCH, M.D., HOWARD B. GOLDSTEIN, M.D., HARVEY PECK, M.D., AND IRA S. JAFFREY, M.D.

Abstract

A case of fibrosarcoma arising from the sacral dura in a 26-year-old woman with von Recklinghausen's disease is reported. The x-rays, computerized axial tomography, myelograms, and operative findings are described. A brief review of the world literature is presented.

Introduction

In patients with neurofibromatosis, there is an increased incidence of soft tissue sarcomas that do not originate from the nerve sheath (1, 2). Tumors which are obviously not of Schwann cell origin can be indistinguishable from a nerve sheath fibrosarcoma, the most common type of malignant neoplasm found in association with von Recklinghausen's disease; these lesions are highly malignant and tend to recur locally as well as metastasize. Fibrosarcomas arising from the spinal theca have been reported only occasionally in the world literature (3).

Case Report

A 26-year-old woman with known stigmata of von Recklinghausen's disease since infancy developed low back pain after being involved in a moving vehicular accident. Periods of remission and exacerbation continued for over two years. Approximately six months prior to admission, she was reevaluated by her family physician for severe pain in the lumbosacral area radiating into the left lower extremity. She was admitted to the hospital by a neurologist following the onset of urinary incontinence.

Physical examination revealed several large café-au-lait spots and multiple small subcutaneous nodules over the trunk and extremities. Significant findings in the neurologic examination were absent ankle jerks, weakness in the left extensor hallucis longus and extensor digitorum longus, and a level of hypesthesia up to the L4 dermatomes. A Foley catheter was in place; cystometry was consistent with a reflex neurogenic bladder.

X-rays of the lumbosacral spine showed a lobulated, lytic lesion of the sacrum at the S2-3 level (Fig. 1). Computerized axial tomography revealed a soft tissue mass filling and enlarging the sacral canal (Fig. 2). Lumbar myelography demonstrated a capping lesion at the L5 level, consistent with a benign intradural tumor (Fig. 3).

Neurosurgical consultation was requested. The patient was taken to the operating room and underwent lumbar laminectomy and total excision of a firm spherical tumor of the sacrum, 6cm in diameter and attached to the theca. The dura was then opened up to the L3 level. A solid cylin-

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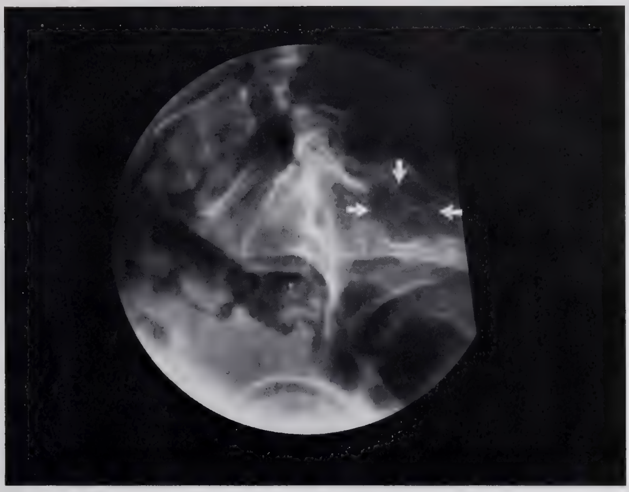

FIG. 1. Lateral coned spot view of L5-Sl region, showing a destructive lesion in the sacrum (arrows). Note some condensation in the anterior edge of the mass, an indication of slow expansile growth.

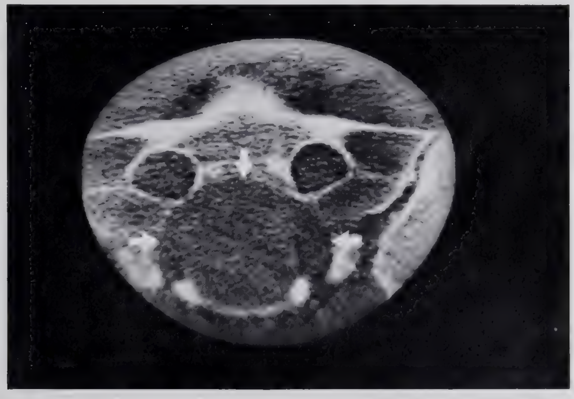

FIG. 2. Computerized axial tomographic section through the upper sacrum. Note intact well defined margins (arrows), suggesting an expanding rather than infiltrating process.

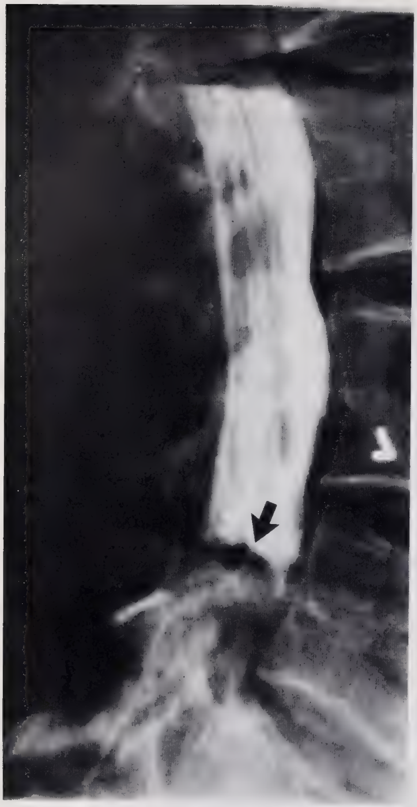

FIG. 3. Myelography with ethyl iodophenylundecylate. Note complete obstruction to the caudad flow of contrast material (arrow). The margins are not irregular, nor is the surrounding bone infiltrated.

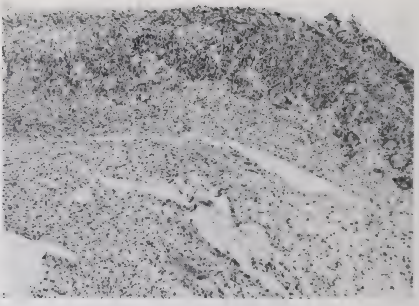

FIG. 4. Highly cellular intradural tumor containing peripheral areas of edema, necrosis, and congestion. (H + E 25×).

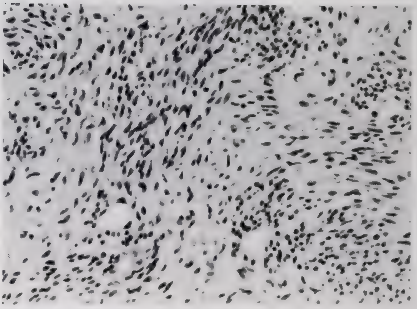

FIG. 5. Spindle-shaped neoplastic cells with bipolar processes are shown arranged as irregularly parallel interweaving bundles (H + E 400×).

der of neoplastic tissue about 2.5cm in diameter and 4cm in length was completely removed; attachments to the cauda equina were dissected under microscopic technique. No nerve roots were sacrificed.

Histologic sections revealed a highly cellular neoplasm with well differentiated spindle-shaped cells (Fig. 4). Bipolar processes, deeply stained nuclei, occasional mitoses, and interlacing fascicles were regular features (Fig. 5). The microscopic findings were consistent with a fibrosarcoma of nonneurogenic origin.

Postoperatively, she became fully ambulatory and regained bladder control. Chemotherapy with doxorubicin was begun, and cobalt radiotherapy up to a total of 4000 rads was planned. Four weeks after discharge, weakness in the lower extremities and urinary incontinence recurred, and she was readmitted to the hospital.

Repeat myelography demonstrated a complete block above the limits of the decompressive laminectomy at the L3-4 level (Fig. 6). She was immediately taken to the operating room and reexplored. The laminectomy was extended up to the L1 level. Neoplastic tissue was found invading the paraspinal muscles and ligaments (Fig. 7). The dura was opened, and solid tumor was now observed to fill the subarachnoid space with extensive envelopment of the conus medullaris and cauda equina (Fig. 8). The sarcoma could not be resected; the dura was not closed in order to provide further decompression.

During the first postoperative week, the strength in her legs improved. The patient remained incontinent and was markedly anorexic. On the tenth hospital day, there was sudden onset

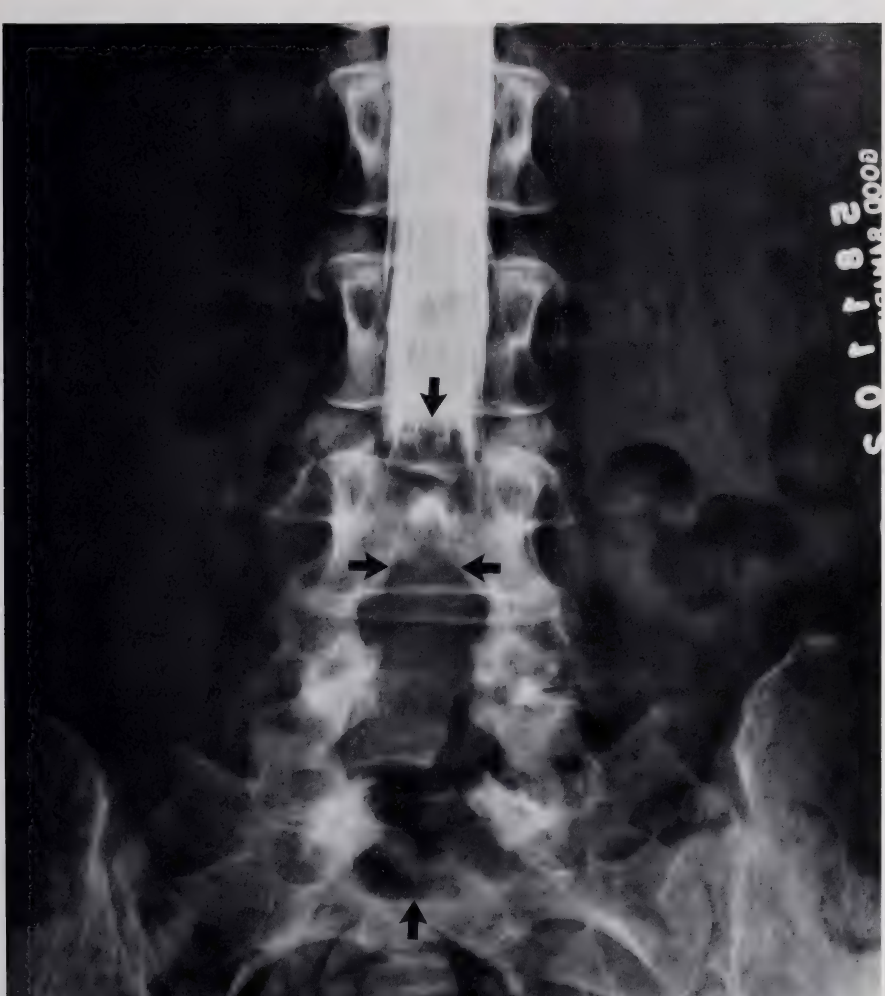

FIG. 6. Second myelogram showing a complete block at L3-4 level (upper vertical arrow). Note vertical striations at the cephalad end of the process suggesting splaying and fixation of nerve rootlets. The previous laminectomy is documented from L4 (upper horizontal arrows) to S2 (lower vertical arrow).

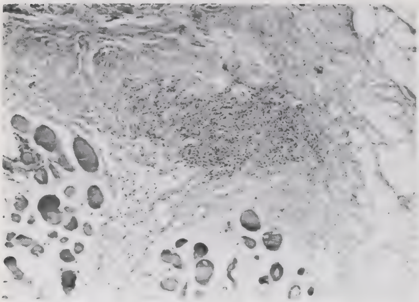

FIG. 7. Extradural infiltration of neoplasm into paravertebral tendinous tissue (H + E 25×).

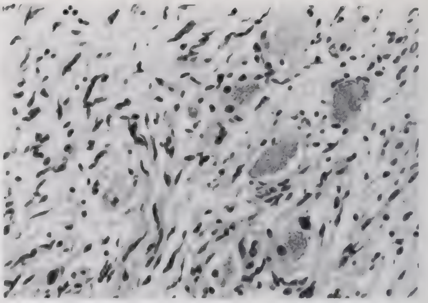

FIG. 8. Invasion of neural tissue by neoplastic cells (H + E 400×).

of quadriplegia and respiratory distress; and she expired.

Discussion

Neurofibromatosis is characterized chiefly by tumor formation of peripheral nerves and pigmentary changes in the skin. Malignant neoplasms of nerve sheath origin occur sporadically in patients with von Recklinghausen's disease; but rarely, if ever, does the tumor develop within a benign schwannoma. The terms malignant neurilimoma, neurogenic sarcoma, neurofibrosarcoma, and malignant schwannoma have arbitrarily and incorrectly been applied to many neoplasms arising from the somatic soft tissue and secondarily involving the central nervous system (4).

One of the most serious complications of von Recklinghausen's disease is sarcoma. The true incidence of neurofibromatosis is difficult to establish since many abortive forms of this neurocutaneous syndrome go unreported. The reported incidence of all types of sarcoma in patients with von Recklinghausen's disease ranged from 1% to 16% (1, 2, 4). Primary sarcomas of the spinal meninges are infrequently seen in neurosurgical practice, and no previous report of a fibrosarcoma of the sacral dura in a case of neurofibromatosis has been found in the world literature.

Acknowledgments

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Brainstem Metastasis Presenting as Cranial Nerve Palsy: Diagnosis by Computerized Axial Tomography

Jeffrey A. Cohen, M.D., Arthur D. Kay, M.D., and I. S. Song, M.D.

Abstract

Intracranial metastasis are common central nervous system neoplasms ~~in~~ which usually occur supratentorially or in the cerebellum. Brainstem metastases are rarer and more difficult to diagnose. The patient in this report had an unusual clinical presentation which is contrasted with prior reports. The value of computerized axial tomography in the early diagnosis of intracranial metastatic disease is discussed.

Introduction

Intracranial metastases comprise 6% of all brain tumors (1) and are found in 15%–20% of autopsies performed on patients with neoplasia. Brainstem metastases account for 5%–12% (2, 3) of all intracranial metastatic lesions. Isolated brainstem metastatic lesions usually are rare (2). Past reports have dealt with the difficulty in the diagnosis of these lesions (2–4). The development of computerized axial tomography (CAT) has improved the ability to investigate metastatic lesions of the brain (1, 5).

Recently, we have had the opportunity to care for a patient whose course was unlike prior reported cases of brainstem metastasis. The features of this case are discussed in light of the value of computerized axial tomography.

Case Report

A 61-year-old, right-handed male was admitted to the Neurology Service of The Bronx Veterans Administration Medical Center with a chief complaint of unsteadiness of gait, slurred speech, and a twenty-pound weight loss over a six-month period.

A resection of the left upper lobe of the lung for removal of an epidermoid carcinoma was performed six months prior to the present admission. At the time of surgery, there was no involvement of the surrounding lymph nodes. One month postoperatively, the patient noted unsteadiness of gait and slight slurring of his speech. Four months later, he was admitted for evaluation of dizziness, weakness, and insomnia. Neurologic examination at that time was reported to be within normal limits. Radiographs of the skull and technetium brain scan were interpreted as normal.

The patient's initial admission to The Bronx Veterans Medical Center was one month later after repeated episodes of falling. On admission, the general physical examination revealed an ill-appearing thin male. A left thoractomy scar was present; auscultation demonstrated decreased breath sounds at the left base. On neurologic examination, the patient was alert and cooperative; cranial nerve function was intact with the exception of moderately dysarthric speech. Motor function, deep tensor reflexes, and sensory testing were normal. Coordination testing demonstrated no defects on finger to nose and heel to shin testing. The patient's gait was narrow based but unsteady with a tendency to fall to either side. Romberg's sign was absent.

Admitting laboratory studies: Complete blood count, routine chemistries and urinalysis were normal. Chest x-rays were unchanged.

During the first days of his hospitalization, the patient's speech became more dysarthric. In addition, he developed nasal regurgitation of both liquids and solids. Computerized tomography of the

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head was performed. The precontrast study showed an area of decreased attenuation at the level of the pons, midbrain, thalamus and the surrounding cerebellar hemispheres. There was an area of slightly increased attenuation at the mid portion of the pons. (Fig 1). The postcontrast study revealed a very densely enhancing, well-circumscribed mass at the level of the pons (Fig. 2) with surrounding decreased attenuation representing adjacent edema (Fig. 3). An additional contrast enhancing lesion was seen in the right frontal cortex (Fig. 4).

The patient was started on steroid therapy (dexamethasone, 16 mg/day) and whole brain cobalt irradiation (total dosage 4500 R). He was noted to have less dysarthria, dysphagia, and unsteadiness over the course of therapy. The patient improved to a level at which he was able to receive his radiotherapy as an outpatient. Followup examinations at one and two months later revealed only mild dysarthria.

Discussion

Brainstem metastases are uncommon; they constitute about 5%−12% of all intracranial metastases. In the past, studies of brainstem metastasis required pathologic material; antemortem diagnosis was fraught with inaccuracy. In Hunter's series (3), only two cases were diagnosed correctly prior to death. In the majority of patients, brainstem signs were labelled as false localizing signs, and thought to have no bearing on the diagnosis. Usually, brainstem metastases do not occur in isolation but rather in conjunction with a supratentorial lesion. In the majority of cases with multifocal metastases, the cerebral symptoms predominate.

Since the development of computerized axial

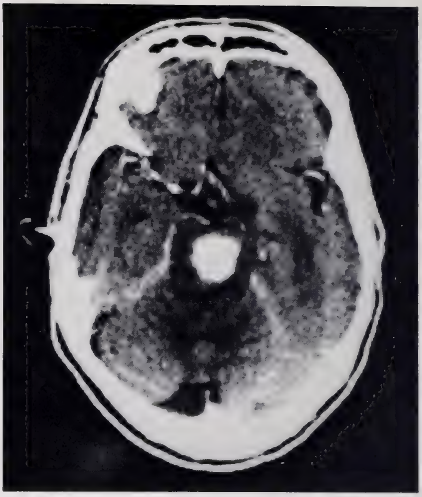
FIG. 2. Postcontrast scan through the pons shows densely enhancing mass at the center with surrounding edema in the pons and cerebellum.

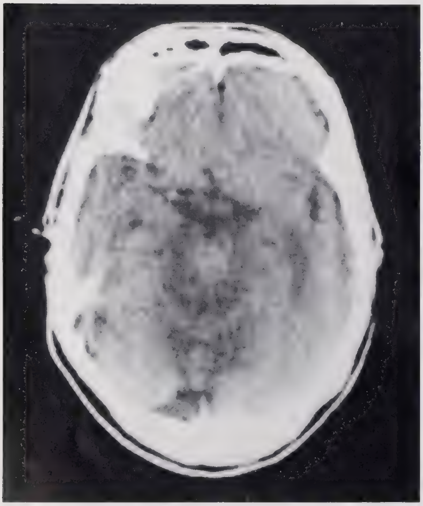
FIG. 1. Precontrast scan through the pons shows decreased attenuation in the pons and cerebellum, with an area of increased attenuation at the center of the pons.

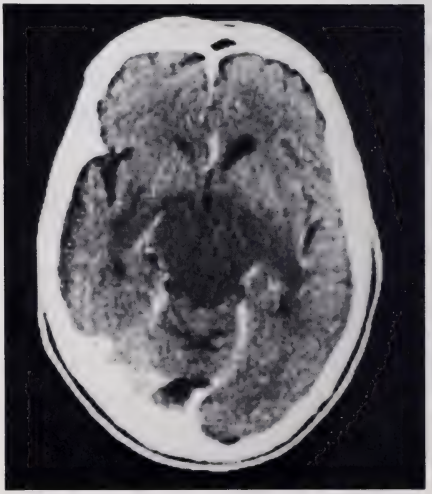
FIG. 3. Precontrast scan (above the level of Figures 1 and 2) shows large area of decreased attenuation at the midbrain and thalamic area. The third ventricle is compressed.

tomography, the demonstration of intracranial metastatic disease has been markedly facilitated. As scanners with greater degrees of resolution become available, lesions within the posterior fossa not previously detectable can be seen without angiography or pneumoencephalography.

As a result, it is useful to evaluate the present case in view of prior experience with brainstem metastases. The most frequent primary tumor is squamous cell carcinoma of the lung (1, 3). The posterior cavity is more likely to be involved with carcinoma of the lung (3). The interval between discovery of the lung carcinoma and the appearance of metastatic disease is usually short (2–4). Our patient's symptoms began one month after surgery. Four months postoperatively, the patient had increasing difficulties, yet the neurologic examination and technetium brain scan were interpreted as normal. Six months postoperatively, the patient was noted to have dysarthria and unsteadiness of gait. After two days of hospitalization, the patient developed another finding of brainstem dysfunction, difficulty with swallowing which suggested involvement of cranial nerves IX and X.

The computerized axial tomograms show involvement of the neuraxis from the diencephalon to the medulla with an additional lesion in the right cerebral hemisphere. In this situation, the cerebral lesion produced no overt clinical symptomalogy (for example, visual disturbance, motor deficit, or sensory disturbance); the brainstem involvement predominated. The clinical presentation of isolated dysarthria and dysphagia is uncommon. The cranial nerve deficits in most prior reports were accompanied by long tract signs (motor or sensory disturbances) (2–4). Our patient did not demonstrate any symptoms of increased intracranial pressure (headache, nausea, vomiting or confusion) which previous authors have observed as common (1, 6). Despite the extent of the lesion, the patient's clinical symptoms and signs were localized to a small portion of the brainstem. The investigation of the patient's complaints was easily accomplished with computerized axial tomography. The patient's dysphagia disappeared after whole brain irradiation and steroid medication.

In addition to its diagnostic capability, computerized axial tomography can monitor the results of treatment in metastatic brain lesions. The decrease in size of the tumor mass, its surrounding edema, and the lesion's enhancement may be easily followed. Computerized axial tomography can indicate whether clinical worsening of a patient may be due to a new metastasis, enlarging tumor mass, hemorrhage, hydrocephalus, or infarction (5). Third and fourth generation scanners will increase the accuracy of the investigation of the posterior fossa. The patient with a brainstem lesion and mild neurologic findings may be diagnosed sooner than with the prior use of nuclear brain scanning, angiography, pneumoencephalography or even the earlier generations of scanners.

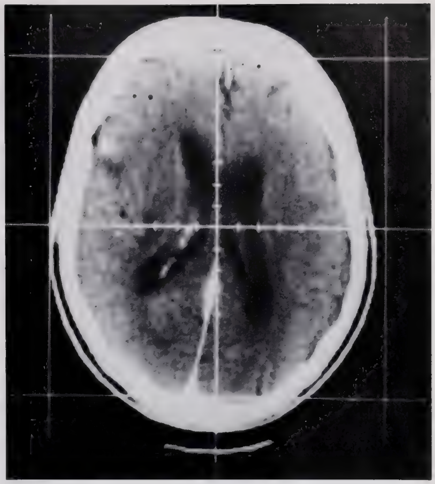

FIG. 4. Postcontrast scan at the level of the lateral ventricle shows an enhancing lesion in the right frontal cortex with mass effect compressing the lateral ventricle.

As the medical and surgical treatment of neoplastic disease improves, computerized axial tomography will prove to be an ideal instrument for the detection and monitoring of intracranial metastasis. The institution of earlier treatment of intracranial metastasis may change the generally poor prognosis for long term survival of patients (6).

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Ewing's Sarcoma of the Mandible

JANINE ZAMOR, M.D.

Abstract

Ewing's sarcoma of the mandible is considered a rare tumor. A growth in this location is more likely to be interpreted clinically as inflammation or metastatic tumor than as a primary neoplasm. Morphologic evidence, combined with radiological assessment of the entire skeleton, showed this case to be a unicentric focus of Ewing's sarcoma within the mandible.

Clinical History

A 13-year old healthy boy presented with a slowly enlarging, slightly tender mass of the left jaw, present for one year. A loose second molar in the left mandible, noted by his dentist, was thought to be the cause of the pain. Radiographs demonstrated a 6 cm mass in the inner aspect of the left mandible with limited erosion of the inner cortex and lifting of the periosteum. A skeletal survey was negative. In addition, no lesions could be demonstrated, either clinically or radiologically in other organs. The loose tooth was removed at another institution. Friable dark red soft tissue adherent to the tooth socket was histologically examined and interpreted as hemangiopericytoma, although consultants favored the diagnosis of granulation tissue. There were no systemic manifestations of disease.

The mass continued to enlarge and the patient was admitted to The Mount Sinai Hospital. A hemi-mandibulectomy, with resection of the tumor was performed. The surgical specimen was received as several fragments; two of bone, three of friable brownish-red soft tissue, as well as two lymph nodes from the neck, a submaxillary gland and three teeth (one molar and two bicuspids).

Pathology

The two osseous parts were flat, slightly curved and irregularly quadrangular, 4 and 5 cm in greatest dimension respectively and 0.2 cm thick. One fragment had a thinned area within which there was a multiloculated cavity containing dark red friable material adherent to the inner surfaces of the small cysts. The soft tissue parts, varying from 2 to 5 cm, were irregularly shaped and focally hemorrhagic.

The submaxillary glands, the two regional lymph nodes and the teeth were grossly and microscopically unremarkable.

Histopathology

Tumor was noted in the disrupted regions of the bone and in two of the irregular soft tissue fragments. The tumor consisted of closely packed broad sheets of small, uniform, round cells separated by slender partitions of well-vascularized connective tissue (Fig. 1). The tumor invaded the medullary cavity and infiltrated the periosteal soft tissue. Cytoplasm of tumor cells was scant with indistinct cell boundaries. In contrast, the nuclei were well defined with occasional discrete, regular infoldings. The chromatin was sparse. A few nuclei contained nucleoli. The periodic-acid-Schiff reaction, after tissue incubation with diastase, demonstrated abundant glycogen within tumor cells (Fig. 2). A few reticulin fibers were in the stroma, but not around individual tumor cells.

Electron Microscopy

1 mm^3 samples of formalin-fixed tumor tissue were washed in several changes of phosphate buffer, and post-fixed in 2% gluteraldehyde, followed by 1% osmium tetroxide in phosphate buffer. Dehydration of the tissue fragments was carried out with graded alcohols and the tissue was embedded in Epon.

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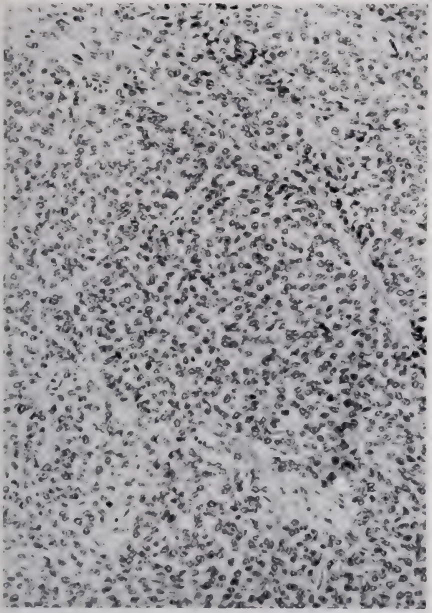

FIG. 1. Low power photomicrograph of a section of tumor showing uniformity of the small round cells. Blood vessels are evident in the fine fibrous tissue strands. (Hematoxylin and eosin, 40×)

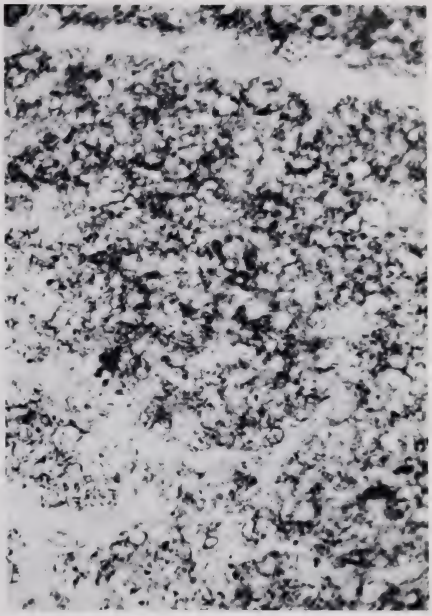

FIG. 2. Glycogen is abundant in the tumor cells and appears as dark-staining granules with the periodic-acid-Schiff reaction. (PAS, 200)

Small cells with scanty cytoplasm with few identifiable mitochondria and ribosomes were seen (Fig. 3). There was no surrounding basement membrane, but a well defined plasma membrane. The nuclei were regular and oval or indented and had fine dispersed chromatin, mainly at the periphery. The nuclear membranes were well defined. Nucleoli were not seen. A few cells had cytoplasmic glycogen granules.

Discussion

Ewing's Sarcoma mainly involves the long tubular bones of limbs and the pelvis, less frequently the ribs, and rarely the small bones of extremities, vertebrae or head and neck (1, 2). Grossly, Ewing's Sarcoma usually manifests as a very soft and friable, gray-white or gray-red mass with areas of fibrosis and hemorrahagic necrosis (2, 3). Ewing's Sarcoma consists of small rounded closely packed cells two to three times the size of lymphocytes, forming sheets, or sometimes cords or nests and separated by fibrous septa (3–5). Mitoses are generally present but not abundant. Most observers agree that cell membranes are indistinct, cytoplasm scant, nuclear membranes well defined and nucleoli scarce. Glycogen is readily demonstrable in the tumor cells (3, 5). Reticulum is not a component of the tumor itself, though it is seen in fibrous trabeculae and around blood vessels. Our case fully meets these criteria.

The ultrastructural features of Ewing's Sarcoma have been demonstrated (6, 7), and include cells with well defined monolayered plasma membrane and scanty cytoplasmic organelles. Free ribosomes are associated with rough endoplasmic reticulum and there are isolated Golgi complexes. The nuclear outlines are regular or occasionally invaginated and the chromatin scarce and marginal. The nuclei contain one or two nucleoli. Glycogen is usually abundant but may be scant in formalin-fixed tissue.

Mandibular Ewing's Sarcoma is rare (8, 9). Geschickter and Copeland (1949) described 11 cases involving the mandible in a series of 126 cases of Ewing's Sarcoma (10). Eight additional cases were reported by Potdar in 1970 (11). Patients with Ewing's Sarcoma have a poor prog-

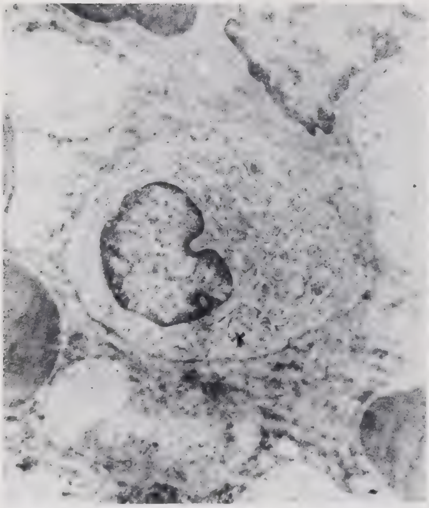

FIG. 3. Electron micrograph showing unimpressive tumor cell with distinct outline, slightly indented nucleus and no nucleolus. A few mitochondria and profiles of rough endoplasmic reticulum are identifiable. Glycogen is indistinct.

nosis. The 5-year survival is less than 10% (12). A greater number of 5-year survivors was in those patients with tumors arising in the long tubular bones and mandible where, presumably, diagnosis and treatment were facilitated. A similar positive correlation between survival and peripheral locations of tumor (mandible or below-knee or elbow) was documented by Pomeroy and Johnson (13). Irrespective of the tumor site, however, the aggressive use of adjuvant chemotherapy seems to have improved the overall survival of patients with Ewing's Sarcoma (14).

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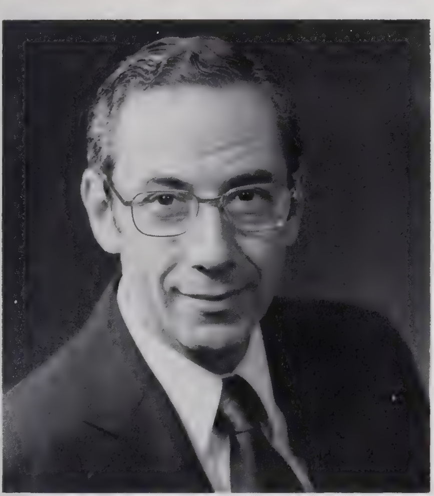
Arthur H. Aufses, M.D. Receives Coveted Golden Cane Award

Editorial Note: Because of the history and honor associated with this award, The Mount Sinai Journal of Medicine's editorial staff believe that our readers would enjoy reading the comments made during the presentation. The Journal staff joins with Drs. Bender and Silver in congratulating the new recipient, Dr. Arthur H. Aufses.

David A. Dreiling, M.D.
Editor-in-Chief



Presentation

Dr. Sol Silver and I, former recipients of the Golden Cane Award, have selected the next "carrier" of the cane. Most of you are probably not familiar with this award because it has been made so infrequently. It was an old English tradition, which began in the 17th century and continued until 1823. Dr. B. S. Oppenheimer, Chief of the first Medical Division at The Mount Sinai Hospital, revived this custom at our institution.

It was a common practice in England to carry a cane, particularly by physicians. It was not unusual for the handle of the cane to have a hollow receptacle which held fragrant herbs or perfume so that the scent might counteract the often malodorous pollutants of the London environment, particularly in areas surrounding the sick and dying in hospitals and in the homes of the less fortunate.

The history of the golden headed cane, which was carried by a series of distinguished physicians, began early in the 17th century. It was first carried by a Dr. Radcliffe from 1689 to 1714 and it accompanied him on many consultations. He was one of the most renowned physicians of his day and was sought by royalty for his medical skills. He treated King William III for asthma with success, but he could not cure the fatal smallpox of Queen Mary. Radcliffe explained the medical failure with the excuse, used to this day, "I have been called too late." He was not the most learned physician but he was the most popular—a situation not unknown in our times. In 1714, Radcliffe passed his cane to Dr. Mead, an accomplished and liberal scholar. He was the most illustrious practitioner of the mid-18th century. Among his patients was Sir Isaac Newton, whom he treated for a bladder stone in 1726. He was also physician to King George II and other members of the royal family. Subsequently, the cane was passed on to other eminent physicians. The last recipient was Dr. Matthew Baillie, a distinguished practitioner and pathologist who died in 1823. Two years later his widow donated the cane to the Royal College of Physicians in London where it has remained until this day.

Dr. B. S. Oppenheimer, who was a great admirer of the English tradition in medicine, was familiar with the story of the Gold Headed Cane. To introduce that custom at our institution, he had an exact replica made of the cane and on April 8, 1941, at an Alumni dinner such as this, he presented the cane to his successor, Dr. Eli Moscowitz. At that ceremony Oppenheimer stated that it was his hope *the cane would be passed to a physician who best represented the personal and professional traditions of the Mount Sinai Hospital,* and that when the holder of the cane became a Consultant, he was to pass it on to one with the same attributes. He did not envision the establishment of the Medical School, where the title of Emeritus is used. Since 1941 the cane has been passed to a line of loyal physicians. On the golden handle is engraved the names of the following holders:

B. S. Oppenheimer to Eli Moscowitz 4-8-41
E. Moscowitz to George Baehr 2-10-42
G. Baehr to Ralph Colp 11-29-52
R. Colp to Solomon Silver 4-17-55
S. Silver to Morris Bender 3-4-72

And now since I am both Consultant and Emeritus (but *not* retired), I will present the cane to the next holder. The decision as to the new recipient, according to custom, is made by the surviving carriers, namely Solomon Silver and myself, and we have chosen a superb and skillful surgeon with excellent clinical judgement, and one who embodies the spirit of Mount Sinai, Dr. Arthur Aufses, Jr. Congratulations, Arthur.

Morris B. Bender, M.D.

Acceptance

I am overwhelmed at this honor, but as you know, I am never speechless. While collecting my thoughts, however, I would like to tell you a story. I left home this morning to enjoy Alumni Day—the scientific program was superb. Those of you who were not there missed a spectacular event—an event that does the participants of the Class of 1982 and Mount Sinai School of Medicine proud. I then attended a superb lunch but felt a little depressed when so many of my former interns got up to get their twenty-five year awards. I then planned to have a ball here this evening watching four outstanding choices get their Jacobi medallions. I am sure that all of you agree with me that the choices could not have been more appropriate.

But back to the story: I was sitting in the auditorium listening to Loren Skeist tell me how to get from a type A personality to a type B personality and realizing that I could probably never make it. At any rate, suddenly I felt a tap on the shoulder and it was Moe Bender. He said, "I have to speak to you," took me to an empty row and said, "I'm sitting with you this evening." I replied, "Yes, I know." He gave me a piece of paper and said, "Read this, and don't tell anybody. I'll see you this evening" and left. And as you can see by the look on Harriet's face, I didn't even tell her.

I read the paper and was stunned. "This" was a copy of Moe's speech. I am indebted to Moe for the warning, however short, because I suspect if I had been sitting in my seat and heard my name called out of the blue, someone would have had to perform a Heimlich maneuver at least and CPR at worst. I also had some time to think about what I might say tonight.

The names on this cane—Oppenheimer, Moschowitz, Baehr, Colp, Silver, and Bender are the giants of Mount Sinai. I feel like a pigmy beside them.

I have said it before—I am what I am because of Mount Sinai. If I have accomplished anything here, it is because of all of you. I have been blessed with a superb group of people to work with—our house staff (and many of our chief residents are here tonight), the Attending Staff of the Department of Surgery—these are the greats of Mount Sinai. Then, the administration—Sam Davis, Barry Freedman, Tom Chalmers and Sherman Kupfer—make it easy to do a job. I was fortunate to have a heritage of Aufses' here ahead of me. And then there's Harriet. What can I say about her that all of you don't already know—when you have a woman like that at your side, you can climb mountains.

So I accept the gold headed cane, not as a personal achievement but as a symbol of what Mount Sinai means to all of us—a superb institution where we can pursue excellence, can take care of our patients, practice outstanding medicine and surgery, can try to advance knowledge, and where we can teach and learn from our students, our residents and each other.

In closing, I want to thank Dr. Bender and Dr. Silver for bestowing this incredible honor upon me. I promise you that I will strive to the utmost to uphold the tradition which you and your predecessors have set.

Thank you very much.

Arthur H. Aufses, Jr., M.D.

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Gastric Cytoprotection

Stanisław J. Konturek, M.D.

Introduction

Prostaglandins (PGs) of the E and A series have been known since 1967 to inhibit gastric acid secretion and to prevent the formation of gastric and duodenal ulcers induced by various techniques. This antiulcer effect of PGs was attributed entirely to their antisecretory property (1). Robert et al (2) observed, however, that aspirin-induced gastric hemorrhagic erosions were prevented not only by certain PGs of the E type which inhibit gastric acid secretion but also by other PGs such as $PGF_{2\alpha}$ or $PGF_{2\beta}$ which do not affect this secretion. Furthermore, gastric lesions evoked by the exposure of gastric mucosa to necrotizing agents such as absolute ethanol, 25% NaCl, 0.6 M HCl, 0.2 N NaOH, acidified taurocholate and even boiling water, were prevented dose dependently by PGs with or without gastric antisecretory activity. This ability of PGs to prevent damage to the gastric mucosa by a variety of agents without reducing gastric secretion has been termed cytoprotection.

In addition to the protective action of exogenous PGs on gastric mucosa (direct cytoprotection), it has been suggested that locally generated PGs may also be responsible for the protective effects of mild irritants (for example, 10% ethanol, 5% NaCl, 0.3 N HCl, 0.07 N NaOH, 5mM taurocholate) applied to the gastric mucosa against the action of corrosive substances. These effects of mild irritants were termed adaptive cytoprotection since it appears to be a localized defensive reaction of the body against the introduction of noxious agents (1, 4, 5).

The purpose of this review is to summarize recent progress in gastric cytoprotection, particularly the involvement of PGs in gastric mucosal integrity, possible cytoprotective effects of other compounds such as antisecretory drugs and gastrointestinal hormones, the mechanisms of gastric cytoprotection and clinical implication of the cytoprotection.

Biosynthesis of PGs in the Gastrointestinal Tract

It has been well known for a long time that PGs of the E and F types can be synthesized in tissues throughout the gastrointestinal tract (6–10). The biosynthesis of PGs and other biologically active compounds such as thromboxanes and leukotrienes starts with the release from the cell membranes of common precursors, 20-carbon polyunsaturated fatty acids. These precursor acids incorporated into the membrane phospholipids are released by enzyme phospholipase A_2 and gain access to the enzyme complexes which are present in greater or lesser amounts in most tissues. The enzymatic metabolism of fatty acids can follow two pathways (Fig. 1). The cyclooxygenase pathway gives rise to the PGs and thromboxanes, while the lipoxygenase pathway gives rise to the leukotrienes and other unsaturated hydroxyacids.

The first PG in the cyclooxygenase pathway is PGG_2, a labile intermediate that can proceed either spontaneously or by a peroxidase to PGH_2 which in turn is quickly converted to thromboxane A_2, PGD_2, PGE_2, $PGF_{2\alpha}$ and PGI_2 (prostacyclin).

Thromboxane A_2 (TXA_2) formed from PGH_2 by an enzyme complex thromboxane synthetase, is very unstable (half life is about 30 sec) under physiologic conditions and is hydrolyzed to the hemiacetal oxane TXB_2, which is then metabolized like the PGs.

An endoperoxide isomerase can convert PGH_2 to either PGE_2 or its isomer PGD_2. The combined action of this isomerase and a reductase yields $PGF_{2\alpha}$. PGE_2 then may undergo dehydration to PGA_2 and isomerization to PGB_2. PGs of E and F

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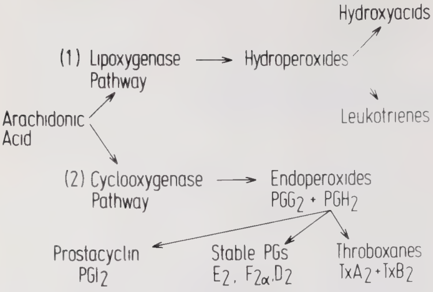
Hydroxyacids
(1) Lipoxygenase Pathway
Hydroperoxides
Leukotrienes
Arachidonic Acid
(2) Cyclooxygenase Pathway
Endoperoxides PGG2 + PGH2
Prostacyclin PGI2
Stable PGs E2, F2α, D2
Throboxanes TxA2 + TxB2

FIG. 1. Arachidonate metabolism via lipoxygenase and cyclooxygenase pathways.

series are relatively more stable but also undergo rapid inactivation, the first step being oxidation of the C-15 hydroxyl by 15-hydroxy PG dehydrogenase. This enzyme, widely distributed in many tissues, particularly in the lungs, is responsible for the inactivation of PGs of E and F series by over 90%−95% in a single passage through the lungs. Intravenously injected PGE_2 or $PGF_{2\alpha}$ is quickly eliminated from the circulation and converted into the major plasma metabolites 15-keto-13,14-dihydro-PGE_2 and 15-keto-13,14-dihydro-$PGF_{2\alpha}$. The plasma levels of these compounds in normal healthy females and males range 5−100 pg/ml. The estimated daily endogenous production of PGE_1 + PGE_2 and $PGF_{1\alpha}$ + $PGF_{2\alpha}$ ranges between 16−292 μg and 50−369 g, respectively (9) (Fig. 2).

PGI_2, one of the most recently discovered PGs (11) formed from PGH_2 by prostacyclin synthetase, is very unstable under physiological conditions (half life is about 2 min.) and hydrolyzes to 6-keto-$PGF_{1\alpha}$. PGI_2 is also a substrate for 15-hydroxy-PG-dehydrogenase but, paradoxically, the dehydrogenation does not take place in the lungs and this argues in favor of PGI_2 being a circulating mediator (12). It is of interest that 15-hydroxy-PG-dehydrogenase is an intracellular enzyme and PGs in the circulation have to be brought into the cell by an active transport system. PGI_2, while a substrate for this enzyme, is not transported by this mechanism in the lungs and this prevents its inactivation during passage through the pulmonary circulation. Unlike PGs of E or F series, PGI_2 is inactivated up to about 80% during the passage through the liver, indicating that PGI_2 generated in the gut may reach the general circulation only in small quantities (13).

The gastrointestinal tract appears to be less active in biosynthesis of PGs than the kidneys and seminal vesicles but more active than most other tissues. Most of the products of arachidonate metabolism have been identified in the gut, the mucosa being more active in the PG biosynthesis than the muscle layer (9, 10). There are marked species variations in the generation of various types of PGs. Quantitatively, the predominant form of PG in human, canine or feline gastric mucosa seems to be PGE_2 (6, 9, 10, 14, 15) whereas, in the rat mucosa, it appears to be PGI_2 (16, 17). Gastrointestinal mucosa exhibits a very high ac-

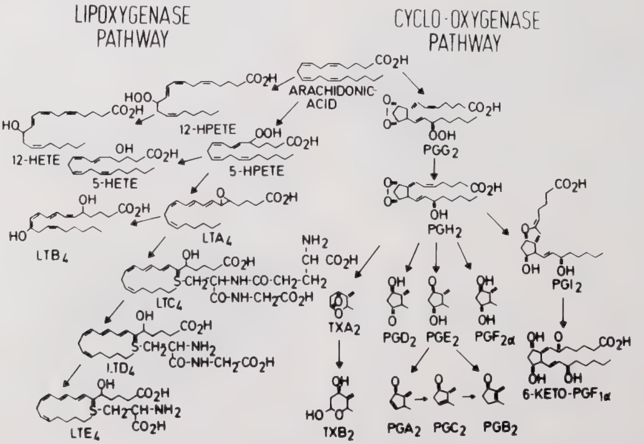
LIPOXYGENASE PATHWAY
CYCLO-OXYGENASE PATHWAY
ARACHIDONIC ACID
12-HPETE
12-HETE
5-HPETE
5-HETE
LTA4
LTB4
LTC4
LTD4
LTE4
PGG2
PGH2
PGI2
6-KETO-PGF1α
TXA2
TXB2
PGD2
PGE2
PGF2α
PGA2
PGC2
PGB2

FIG. 2. Major products of arachidonate metabolism via cyclooxygenase and lipoxygenase pathways.

tivity of the PG metabolizing enzymes, 15-hydroxy-PG-dehydrogenase and PG- Δ^{13}-reductase (18), which convert PGs to stable and inactive 15-keto-13,14 dihydro-PG metabolites. In contrast to natural PGs, some synthetic analogs of PGE_2 with methyl groups at either C_{15} or C_{16} (19) were found to be resistant to the enzymatic degradation. They were reported to be 50–100 times more potent and longer acting agents than native PGE_2. Unlike natural PGs, which are active only after parenteral administration, methylated PGE_2 analogs are effective both after parenteral and oral administration.

The details and significance of the lipoxygenase pathway are still being studied. No rings are formed, but as in the cyclooxygenase pathway, the first products formed are hydroxyperoxides, which are then converted by peroxidases to the corresponding hydroxides and finally to leukotrienes. LTA_4 is a cyclic endoperoxide derived 5-HPETE which then can either be further oxidized at the 12-position to LTC_4 or conjugated to the -SH of glutathione. LT_4 is further metabolized to LTD_4 and LTE_4 by successive loss of glutamine and glycine from the glutathione (Fig. 2).

Arachidonate metabolism can be inhibited by glucocorticoids which suppress phospholipase A_2 by promoting synthesis of a peptide inhibitor, thus preventing liberation of arachidonic acid from phospholipids (20). Thus glucocorticoids inhibit both cyclooxygenase and lipooxygenase pathways. Aspirin and other so-called nonsteroidal antiinflammatory compounds inhibit the cyclooxygenase pathway both *in vitro* and *in vivo*. Indomethacin, one of the more potent inhibitors, has become a widely used pharmacologic tool but it may have many other pharmacologic actions other than inhibition of the cyclooxygenase (21).

Role of Endogenous PGs in Gastric Secretion and Mucosal Blood Flow

Because certain PGs are generated in large amounts in the gastric mucosa, it is suggested that they play a physiologic role in regulating gastric secretion. This concept was supported by the observation that the stimulation of gastric secretion by various secretagogues (insulin, gastrin, histamine) resulted in increased release of PGs in gastric juice (6, 22, 23) suggesting that this release is part of a feedback mechanism preventing excessive secretion of gastric acid. Arachidonic acid, the precursor of PGs given directly into an artery supplying the stomach or topically to the gastric mucosa in dogs, inhibited acid secretion stimulated by histamine or pentagastrin (24, 25). Pretreatment with indomethacin, a potent inhibitor of cyclooxygenase, abolished the inhibitory action of arachidonic acid probably due to inhibition of endogenous release of PGs (25).

Inhibitors of cyclooxygenase such as aspirin or indomethacin by themselves did not affect gastric secretion, indicating that endogenously released PGs do not play any significant role in the control of gastric acid secretion. Inhibition of PG biosynthesis by aspirin or indomethacin caused, however, a 30%–50% reduction in gastrin mucosal blood flow in dogs and rats (25–28) while exogenous PGs, particularly PGI_2, increased this flow in nonstimulated stomach (29). These observations are consistent with the hypothesis that endogenous PGs within the gastric mucosa contribute to the maintenance of its blood flow in the resting stomach. With respect to the vasodilation associated with stimulated gastric acid secretion, endogenous PGs also were suggested to contribute to this vasodilation. Exogenous PGs, particularly PGI_2, was reported to increase mucosal blood flow while inhibiting histamine-induced acid secretion (30). Inhibitors of PG biosynthesis were found to decrease mucosal blood flow without affecting stimulated gastric acid secretion (26). These findings support the concept that endogenous PGs may contribute to the vasodilation associated with stimulated acid secretion. Confirmation will depend on direct measurement of specific endogenous PGs and their metabolic products within the resting gastric mucosa and during stimulated or inhibited gastric acid secretion.

Antiulcer Effects of Prostaglandins

It was anticipated that antisecretory PGs would exert antiulcer activity. This property was tested in various experimental models in animals and in humans. Antisecretory PGs, natural and synthetic analogs, administered either orally or parenterally to various species prevented the formation of experimental duodenal ulcers induced by infusion of secretagogues (31) or gastric ulcerations produced by pylorus ligation (Shay rats) (32), administration of steroids (steroid-induced ulcers) (33) or nonsteroidal antiinflammatory compounds (NOSAC) such as aspirin or indomethacin (15, 17, 33–35), and exposure to stress such as forced exertion or restraint (36, 37). This antiulcer activity of PGs, attributed to their antisecretory action, was observed not only in laboratory animals but also in humans with gastric or duodenal ulcers (38). Recent multicenter double-blind trials in patients with endoscopically proven duodenal ulcers conducted with oral administration of PGE_2 methylated analogs showed that they accelerate the healing rate of ulcers. Some studies (39) indicated that the hypersecretion in duodenal ulcer patients may result from the deficiency of PG biosynthesis but the possible role of PGs in the pathogenesis of peptic ulcer disease remains to be established.

Gastric Lesions Caused by Nonsteroidal Antiinflammatory Compounds (NOSAC) and Mucosal Generation of PGs

Exogenous PGs, capable of preventing gastric mucosal lesions induced by inhibitors of cyclooxygenase, suggests that PGs may play an important role in maintaining mucosal integrity and in the protection of the mucosa against potentially noxious agents. These inhibitors, including aspirin, indomethacin, ibuprofen and phenylbutazone, are the most common agents that cause gastrointestinal intolerance. They may produce gastric lesions characterized by bleeding, focal necrosis and frank ulcerations both in animals (2, 15, 17, 34, 40–43) and in humans (14, 44). The mechanism of gastric mucosal damage by drugs inhibiting cyclooxygenase is unknown but it has been hypothesized that it may be due to the withdrawal of normal protection provided by endogenous PGs (1).

This hypothesis was tested by direct measurement of the generation of PGs in the gastric mucosa of rats (17, 43), cats (15), and humans (14, 44–46). NOSAC drugs, particularly aspirin and indomethacin, were found to induce gastric lesions within a few hours of the intragastric or parenteral administration (17). The incidence and the severity of these lesions in rats were dose-dependent and required the presence of acid in the stomach to develop (17, 40). According to our experience, they appear in rats as multiple bleeding ulcerations in oxyntic mucosa with sparing of the non-acid secreting forestomach and antrum. NOSAC agents can also produce typical gastric lesions in other species, such as dogs and cats (15, 47), the ulcerogenic propensity depending on the dose employed, the time of administration, and the degree of gastric acidification or gastric acid secretion. This confirms an important role of acid in the development of gastric mucosal lesions. This can be explained that unionized aspirin diffuses from the acid content of the stomach through the mucosa, accumulates within the epithelial cells because of the high pH, and disturbs the mitochondrial phosphorylation and cell buffer system resulting in the cell injury (47).

Direct measurement of the mucosal PGs in the rat stomach exposed to aspirin given parenterally or intragastrically together with acid solution, provided evidence that aspirin causes a dose-dependent decrease in mucosal generation of PGE_2- and PGI_2-like activity (16, 17, 43). Because aspirin is known to inactivate irreversibly the PG synthetase system (21) it is reasonable to assume that the observed gastric mucosal lesions induced by aspirin are due to a deficiency of mucosal PGs. This notion is supported by previous demonstration that naturally occurring PGs in gastric mucosa, such as PGE_2 or PGI_2 given in non-antisecretory doses, are capable of protecting the mucosa from the development of the aspirin-induced gastric ulcers (17, 34, 41). The enhancement of aspirin-induced mucosal lesions by the exposure of the mucosa to acid solution is also closely related to the PG production. Acidification of gastric mucosa, even without aspirin, significantly reduced the generation of PGE_2 and PGI_2 by the mucosa. The combination of gastric acidification plus aspirin rendered the mucosa completely deprived of the ability to synthesize PGI_2, a major product of arachidonate metabolism in the rat mucosa and reduced its capacity to form PGE_2, another important endogenous PG. Thus, the reduction of PG formation by mucosal acidification has a promoting effect on the ulcerogenic action of aspirin (Figs. 3, 4).

In another study on rats with indomethacin, a close temporal relationship was observed between the generation of PGI_2 (used as an index of cyclooxygenase activity) and the formation of gastric

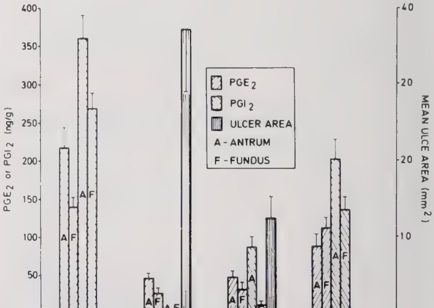

FIG. 3. Generation of PGE_2- and PGI_2-like activity in fundic and antral mucosa of intact rats (control) and after treatment with acidified ASA given intragastrically in various doses. Each column represents mean ± SEM of results obtained from 10 rats.

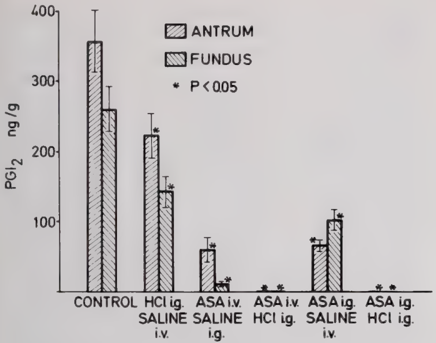

FIG. 4. Effects of ASA administered intravenously (i.v.) or intragastrically (i.g.) in combination with i.g. perfusion of saline or 0.15 M HCl on the generation of PGI_2 in the fundic and antral mucosa of rats. Each column is a mean ± SEM of results obtained from 10 rats.

erosions by this agent (43). These results reinforce the concept that the inhibition of PG biosynthesis is an important process involved in gastric mucosal damage by NOSAC agents.

In the cat's stomach, which generates predominantly PGE_2-like activity, acidified aspirin also reduced the PG formation and produced mucosal lesions located in the antral portion of the stomach. The reason for this localization of the mucosal lesions is unknown but it suggests that in addition to the deficiency of endogenous PGs, other mucosal factors may contribute to the formation of gastric ulcerations (15).

In human gastric mucosa, the generation of PGE_2 was reported to be quantitatively more important than that of other species of PG (6, 8–10, 14). Similarly, PGE_2-like immunoreactivity was found to be the major type of PGs in the gastric juice (48–50). Our recent study (14) on the PG biosynthesizing capability of gastroduodenal mucosa in healthy subjects and duodenum ulcer patients showed that the major species of PGs generated by the mucosa is PGE_2-like activity present in similar quantities in the oxyntic, antral and duodenal mucosa. No significant difference was found in PG generation between healthy subjects and duodenal ulcer (DU) patients, though the later subjects tended to generate slightly larger amounts of PG. This argues against the role of the PG deficiency in the pathogenesis of peptic ulcer disease (39) and remains in agreement with recent findings of Baker et al (49) who showed that the PGE_2 level in plasma of DU patients is not lower than in normal subjects. In addition, the mucosal generation of PGs does not appear to be related to gastric secretory status or serum gastrin concentration. Furthermore, the mucosal generation of PGs remains unchanged during histamine-induced gastric secretory stimulation which is incompatible with the proposed role of locally produced PGs in the control of gastric acid secretion (14) (Fig. 5).

Although it is doubtful whether gastric mucosal PGs control gastric secretion in man, PGs may contribute in maintaining mucosal integrity. We have tested this hypothesis in healthy subjects by administering aspirin in a dose of 2.5 g and measuring the PG generation in gastric biopsy samples before and after this treatment (14). In some healthy subjects and in most DU patients given aspirin, various symptoms of gastrointestinal intolerance including dispepsia, occult bleeding and mucosal lesions were observed. The mucosal damage was accompanied by an increased mucosal microbleeding and DNA loss. Pretreatment with oral PGE_2 (0.5 mg four times daily) before each tablet of aspirin almost completely prevented the formation of mucosal lesions and reduced gastric microbleeding or DNA loss. The protective property of PG does not appear to be a function of its ability to inhibit gastric acid secretion because PGE_2 given orally does not influence this secretion (Fig. 6).

These results do not yet provide definite evidence for the causal relation between the damage of gastric mucosa and the deficiency of mucosal PGs, but it is noteworthy that, for example, paracetamol given in the same dose induces smaller side-effects or gastric mucosal lesions and

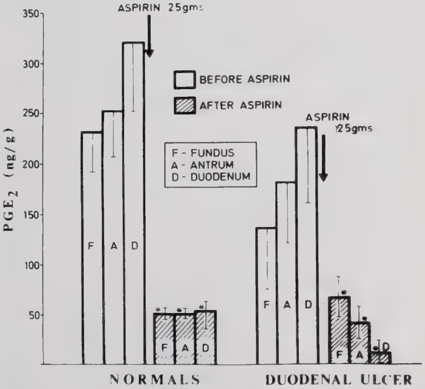

FIG. 5. Generation of PGE_2-like activity in fundic antral and duodenal mucosa of 14 healthy subjects and 13 duodenal ulcer patients before and after ingestion of ASA 2.5 g.

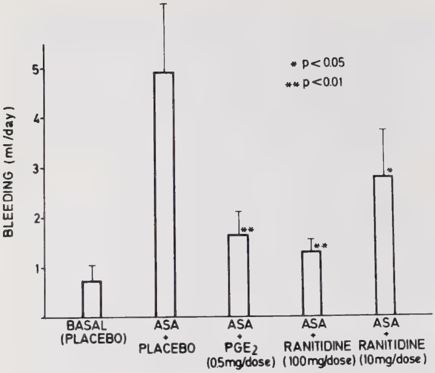

FIG. 6. Gastric microbleeding in eight healthy subjects after placebo and ASA alone or in combination with PGE_2 or ranitidine in a smaller or larger dose. Mean ± SEM of eight tests in eight subjects.

does not cause any marked change in the generation of PGs in the gastro-duodenal mucosa (14).

Gastric Lesions Caused by Necrotizing Agents. Role of Endogenous PGs

A variety of agents administered orally to animals cause immediate massive necrosis of gastric mucosa. Among such agents widely used to produce gastric necrotic lesions is absolute ethanol, 25% NaCl solution or 80 mM acidified taurocholate. Robert et al (3) found that gastric lesions induced by these necrotizing agents can be prevented by the pretreatment of the mucosa with various PGs of A, B, E, F and I series given in a nonantisecretory dose or completely deprived of any antisecretory activity. The cytoprotective dose of inhibitory PGs was shown to be about 100 times smaller than the dose inhibiting gastric secretion. Cytoprotective PGs do not appear to have any particular chemical configuration and the only difference between different PGs is quantitative. The most potent cytoprotectors were methylated PGE_2 analogs, for example, 16,16-dimethyl PGE_2, while non-inhibitory PGs such as $PGF_{2\alpha}$ also exhibited cytoprotection but at much larger doses. Gastric cytoprotection induced by PGs was dose-dependent and several times stronger after oral than parenteral administration of PGs (1, 51).

The finding that exogenous PGs can prevent the formation of mucosal lesions by necrotizing agents does not mean that these lesions result from the deficiency of mucosal generation of PGs. In fact, mucosal generation of PGs in the stomach exposed to 100% ethanol, 25% NaCl or acidified taurocholate, was increased probably due to the cellular trauma and severe mucosal damage (1, 55). Thus, gastric mucosal necrosis caused by strong irritants was accompanied by increased generation of PGs which probably prevented excessive mucosal damage because the suppression of this generation by indomethacin enhanced the severity of gastric lesions. The amounts of generated PGs are obviously not sufficient to provide adequate protection but exogenous PGs given in large amounts are capable of increasing the resistance of the mucosal cells so that they can withstand the contact with highly damaging agents. Thus, cytoprotective PGs do not simply correct a deficiency of these substances but rather increase cellular resistance to the point that gastric damage is limited or does not take place at all.

It is of interest that antisecretory agents such as propantheline bromide or histamine H_2 antagonists, even when applied in large doses causing complete inhibition of gastric acid secretion, did not affect the formation of necrotic lesions in the stomach, whereas small nonantisecretory doses of PG, completely prevented such lesions (1, 3).

Similar protection of gastric mucosa against ethanol injury has been reported recently in man (52). A solution of 40% ethanol reduced transmucosal potential difference (PD) and enhanced epithelial cell shedding and the discharge of mucus from gastric epithelium. Pretreatment of the stomach with 1 mg PGE_2 prevented the ethanol-dependent epithelial cell desquamation (DNA loss) indicating gastric mucosal cytoprotection. It was concluded that gastric cytoprotection by PGE_2 in man might be mediated by stimulation of mucus and bicarbonate production. It is of interest that PGE_2 did not prevent the ethanol-induced fall in PD but the lack of change in PD does not necessarily indicate a lack of alteration in mucosal integrity.

Adaptive Cytoprotection. Role of Endogenous Generation of PGs

Gastric cytoprotection can be evoked not only by exogenous PGs but also by mucosal application of a variety of mild irritants (1, 4, 53). Oral administration of 10%–20% ethanol, 5% NaCl, 5 mM taurocholate prevented massive mucosal damage caused by necrotizing agents such as 100% ethanol, 25% NaCl, 80 mM taurocholate, 0.6 M HCl or 0.2 M NaOH. All these mild irritants, prevented nearly completely the formation of gastric lesions evoked by necrotizing agents and these effects were not different from those of PGs (1, 4).

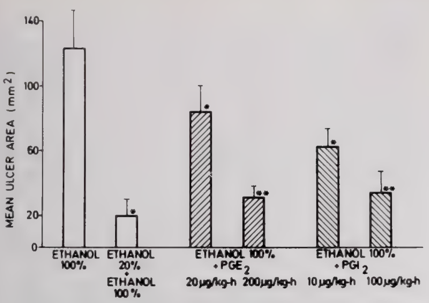

FIG. 7. Mean area of gastric lesions induced by intragastric administration of 100% ethanol and the combination 20% ethanol + 100% ethanol, PGE_2 (20 or 200 µg/kg-h) + 100% ethanol or PGI_2 (10 or 100 µg/kg-h) + 100% ethanol. Mean ± SEM of results from 6−10 rats.

The mechanism of such protection is not obvious but it was suggested that mild irritants exerted their beneficial effects by stimulating the formation of cytoprotective PGs in gastric mucosa. This is supported by the finding that the pretreatment with indomethacin to block the activity of PG cyclooxygenase and to abolish the generation of mucosal PGs, prevented the cytoprotection afforded by mild irritants (51).

These effects of mild irritants called adaptive cytoprotection (1) have also been tested with respect to gastric secretion. Prior exposure of the oxyntic mucosa to mild irritants (for example, 10% ethanol) reduced the net ionic fluxes of H^+, Na^+ and K^+ and the fall in transmucosal PD induced by a second exposure to necrotizing agents. This indicates that after the pretreatment with mild irritants, the mucosa becomes more resistant to the barrier damage by necrotizing agents (54). Such a pretreatment with mild irritants prevented the decrease in the gastric secretory capacity caused by massive mucosal necrosis and speeded the regeneration rate of the mucosal cells (Fig. 7).

As mentioned previously, mild irritants maintain cellular integrity of the gastric epithelium and oxyntic glands presumably via increased formation of cytoprotective PGs in the stomach. This notion has been tested by direct measurement of the mucosal generation of PGs (55). We found that, indeed, mild irritants applied to the gastric mucosa caused a significant increase in the capability of gastric mucosa to generate PGE_2 or PGI_2 and this probably rendered the mucosal cells more resistant to the damaging effect of necrotizing agents. The implication of mucosal PGs in the adaptive cytoprotection was further supported by the finding that indometacin used in a dose which completely abolished the generation of mucosal PGs, tended to prevent the cytoprotective action of mild irritants (Fig. 8).

It is of interest that certain drugs such as salicylate or paracetamol act like mild irritants by stimulating endogenous generation of PGs in gastric mucosa. This explains their protective action against gastric mucosal damage caused by aspirin or ethanol (56).

Cytoprotective Effects of Drugs Inhibiting Gastric Secretion

Although the cytoprotective action of PGs is well established, there are some indications that other drugs, particularly the inhibitors of gastric secretion such as histamine H_2-blockers and anticholinergics and some gastrointestinal hormones may be also cytoprotective. In addition, drugs that promote healing of peptic ulcer without affecting gastric secretion such as carbenoxolone may be classified as cytoprotective. Kauffman and Grossman (57), who used parenteral aspirin to induce gastric ulcerations in rats reported that cimetidine and methylated

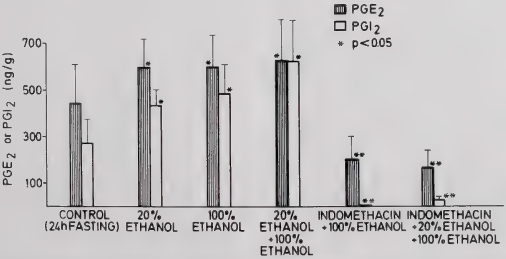

FIG. 8. Generation of PGE_2- and PGI_2-like activity in oxyntic mucosa of intact rats and after treatment with 20% ethanol, 100% ethanol or their combination. Mean ± SEM of results from 6−10 rats.

PGE_2 analog decreased the severity of ulcerations in a dose-dependent fashion. In contrast to experience of Carmichael et al (34), both agents also retained their protective action in the presence of exogenous HCl and pepsin. Guth et al (41) investigated the effects of cimetidine, methylated PGE_2 analogs and the anticholinergic agent probanthine, the formation of gastric lesions in pylorus-ligated rats given topical aspirin and exogenous HCl. All three compounds were found to reduce lesion formation when given in doses considered too low to affect gastric acid secretion and all were considered cytoprotective. We confirmed these observations in rats with gastric lesions produced by acidified ASA administered intragastrically (58, 59). PGs such as PGE_2 or PGI_2, inactive PGI_2 metabolite 6-keto $PGI_{1\alpha}$, $PGF_{2\beta}$, all given in nonantisecretory doses prevented the formation of these lesions. Besides PGs, antisecretory agents such as histamine H_2-blocker ranitidine and probanthine administered in nonantisecretory doses were also cytoprotective. It is of interest that acidified ASA suppressed almost completely the mucosal generation of PGs and the cytoprotection evoked by antisecretory agents occurred when endogenous formation of PGs was almost completely inhibited. Thus endogenous PGs do not appear to mediate gastric cytoprotection by ranitidine or probanthine (Figs. 9, 10).

Further studies are required to resolve the possible cytoprotective effects of gastric secretory inhibitors as compared with these of PGs. If cytoprotection by gastric inhibitors is confirmed, the mechanism involved will not necessarily be the same as that concerned with cytoprotection by PGs. Robert et al (2) reported that cimetidine and probanthine protected the stomach against acidified ASA only when the concentration of acid given together with ASA was within the physiological range (up to 0.15 M HCl). When this concentration was increased above the physiologic range (up to 0.35 M HCl) cimetidine or probanthine ceased to be protective, whereas PGE_2 analog retained its full protective ability. In addition, exogenous PGs were cytoprotective against gastric damage caused by necrotizing substances (e.g. absolute ethanol) but H_2-blockers or anticholinergics given even in large inhibitory doses were completely ineffective in this respect. These results seem to indicate that the spectrum of cytoprotective activity of PGs is much broader than of any other agents. This is confirmed by the findings in animals that exogenous PGs can also protect the small and large intestines from necrosis produced by NOSAC agents, prednisolon or clindamycin (1, 60–63). H_2-blockers and anticholinergics were without any influence on the intestinal lesions.

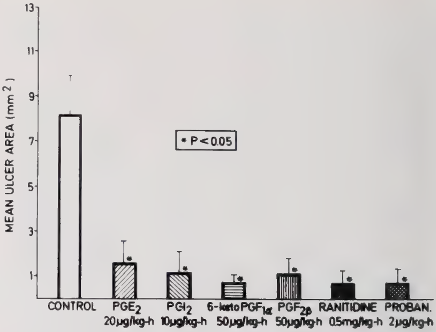

FIG. 9. Mean ulcer area of rats receiving intragastrically acidified ASA alone (control) or after pretreatment with various types of prostaglandins, ranitidine or probanthine, all given subcutaneously in non-antisecretory dose. Mean ± SEM of results from 10–15 rats.

Cytoprotective Effects of Gastrointestinal Hormones

Several gastrointestinal hormonal peptides such as secretin, glucagon, calcitonin, somatostatin or epidermal growth factor (EGF) were reported to inhibit gastric acid secretion and to prevent the formation of experimental ulcerations induced by gastric secretagogues (64–67). The antiulcer effect of these hormones was attributed to the reduction of gastric secretion (somatostatin or EGF) or to the increased alkalization of the duodenum (secretin).

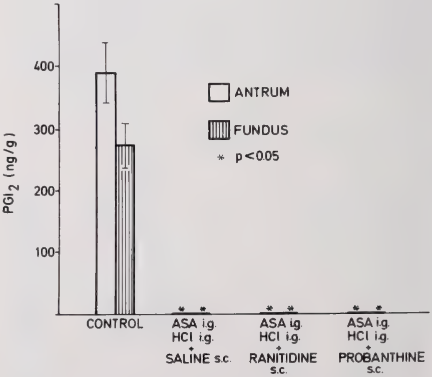

FIG. 10. Generation of PGI_2-like activity in fundic and antral mucosa of intact rats (control) and after treatment with acidified ASA + ranitidine or probanthine as in Fig. 9.

In our attempt to examine the possible cytoprotective action of EGF, a nonantisecretory dose of peptide was used either parenterally or intragastrically against gastric lesions evoked by acidified ASA or ethanol (68). EGF prevented the formation of ASA-induced gastric mucosal lesions without affecting mucosal generation of PGs. This seems to exclude the possible mediation of mucosal PGs in the cytoprotective action of EGF. This study showed that the exposure of gastric mucosa to acidified ASA decreased the synthesis of DNA in the gastric mucosa and that the pretreatment with EGF and cytoprotective PGs prevented the alteration in DNA synthesis. Thus, the common action of both EGF and PGs appears to be the prevention of the suppression in DNA synthesis which renders the mucosa more resistant to the ulcerogenic effect of acidified ASA. EGF is produced by salivary and duodenal glands any may be released into the gut lumen, being resistant to the degradation by gastric or pancreatic proteases (69, 70). This suggests that EGF released into the gut lumen could serve as a natural growth-promoting and cytoprotective factor for the gastrointestinal mucosa (Figs. 11–13).

Somatostatin also reduced the formation of gastric lesions caused by acidified ASA but only when large gastric inhibitory dose of peptide was applied. Similar effects were observed with secretin and glucagon. This suggests that the antiulcer effect of somatostatin, secretin or glucagon probably results from their gastric inhibitory action. Gastrin was found to be without any influence on ASA-induced gastric lesions. None of the gastrointestinal peptide affected mucosal generation of PGs and did not alter the formation of gastric lesions caused by necrotizing agent such as absolute ethanol.

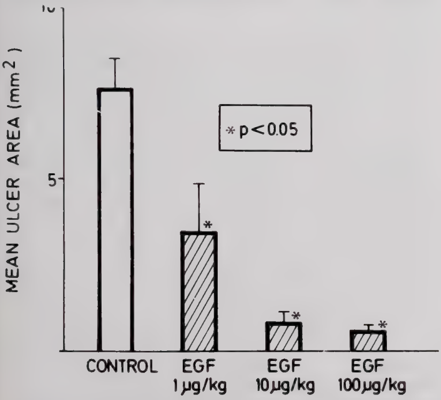

FIG. 11. Mean area of gastric ulcerations induced in rats by acidified ASA without and with pretreatment with EGF given subcutaneously at a dose of 1, 10 or 100 μg/kg.

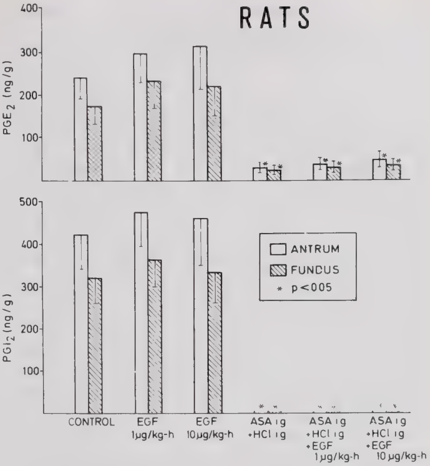

FIG. 12. Mucosal generation of PGE_2- and PGI_2-like activity in intact rats and after intragastric administration of acidified ASA with and without EGF.

Mechanisms of Gastric Cytoprotection

Structure-function relationship. Cytoprotection was demonstrated against mucosal lesions induced by a variety of unrelated agents such as gastric secretagogues, ethanol, NOSAC drugs, cysteamine, prednisolone, etc (1). Similarly there is no particular chemical configuration of cytoprotective compounds which include such substances as PGs, gastric secretory inhibitors or gastrointestinal hormones. There is, however, a qualitative difference between them; PGs are cytoprotective against all kinds of lesions pro-

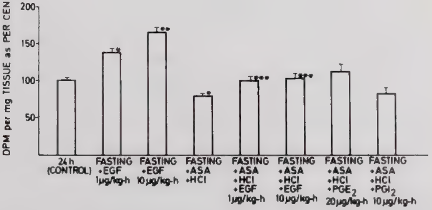

FIG. 13. DNA synthesis in oxyntic mucosa of intact rats and after i.g. administration of acidified ASA without and with pretreatment with EGF, PGE_2 or PGI_2 in animals as in Fig. 12.

duced both in gastric and intestinal mucosa, whereas gastric inhibitors and hormones are effective only against gastric lesions produced by acidified aspirin.

Prostaglandins as supplemental therapy. In case of gastric lesions induced by aspirin and other NOSAC agents, the gastric mucosa is completely depleted of endogenous PGs because of inhibition of PG cyclooxygenase. The lesions develop probably due to deficiency of endogenous PGs and the administration of exogenous PGs may act as a replacement therapy (1, 17, 51). Other necrotizing substances such as ethanol do not cause any deficiency of endogenous PGs and they produce gastric lesions while increasing PG formation (1, 56). In spite of that exogenous PGs in large doses appear to increase cellular resistance and prevent the formation of necrotic lesions.

Cytoprotection induced by gastric inhibitors such as H_2-blockers or EGF can be demonstrated when the generation of mucosal PGs is completely suppressed (58, 68). Thus the cytoprotective effects of these agents appears to be unrelated to mucosal PGs.

Inhibition of gastric acid secretion. As indicated earlier, inhibition of gastric secretion does not seem to contribute to gastric cytoprotection. The fact that cytoprotection can be observed with PGs (6-keto $PGF_{1\alpha}$ or $PGF_{2\beta}$) which do not influence gastric secretion (3, 57, 58) or with gastric secretory inhibitors (EGF, cimetidine, probanthine) given in nonantisecretory doses (57, 58, 68), support the notion that the cytoprotection is unrelated to gastric inhibition. In addition, the gastric cytoprotection is not lost in the presence of exogenous acid in the stomach. Finally, the prevention of indomethacin-induced intestinal lesions by PGs in the region of gut where luminal pH is neutral or alkaline rules out the possible dependence of cytoprotection on inhibition of gastric secretion (61–63).

Stimulation of Mucus and Bicarbonate Secretion

Mucus is secreted continuously by the surface epithelium cells to form the blanket of loose gel adhering to the surface of the gastric mucosa. According to Hollander (71) the mucus layer, the underlying columnar epithelium, the basement membrane and mucosal blood flow, form the barrier for the diffusion of H^+. Until recently there has been a tendency to deny the importance of the mucus barrier to buffer and neutralize influxing H^+. The major functions of mucus have been thought to be the lubrication and protection of the surface epithelium from the mechanical and chemical injury. Heatley (72) suggested that mucus may form the barrier representing a kind of an "unstirred layer" which retards mixing of luminal H^+ with HCO_3^- released by the epithelium. In this way, the bulk H^+ in the lumen may be prevented from the access to the epithelial cells resulting in a pH gradient with low pH levels existing on the luminal side of the mucus barrier and high pH on the cell surface. Recent studies (73) on the structure and properties of mucus emphasize that the effectiveness of the surface mucus gel depends on its depth and the secretion of glycoprotein which must be sufficient to exceed the threshold concentration for gel-formation and to maintain this gel depth. Factors inhibiting mucus secretion are likely to favor ulcerogenesis, whereas factors stimulating the mucus secretion and the formation of the mucus-gel are expected to prevent mucosal injury by noxious agents. Sudden stimulation of mucus secretion by gastric mucosa could explain the cytoprotective effects of PGs (Fig. 14) (74–78).

The secretion of HCO_3^- by surface epithelium cells of antral and oxyntic mucosa is considered to be an active process which can be stimulated by PGs, cholinergic agents, dibutyryl c-GMP, calcium ions and inhibited by atropine, dinitrophenol and acetazolamid (73). The rate of HCO_3^- secretion has been quantitated in experimental animals such as guinea-pig and was found to be about 5–10% of histamine stimulated H^+ output. These amounts of HCO_3^- were thought to be sufficient to prevent luminal H^+ from reaching the mucosal cells provided that mucus barrier has special properties of retarding the passage of H^+ across the layer.

Since NOSAC-drugs and corticosteroids inhibit both mucus and HCO_3^- secretion while PGs appear to stimulate this secretion (73, 79), it has been proposed that the mucus barrier may play a

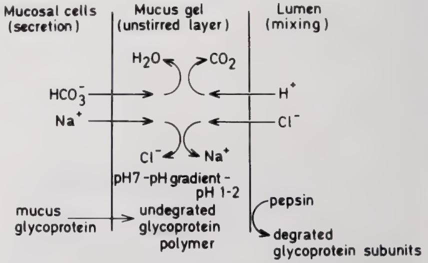
Mucosal cells (secretion)
Mucus gel (unstirred layer)
Lumen (mixing)
H2O
CO2
HCO3-
H+
Na+
Cl-
Cl-
Na+
pH7 -pH gradient - pH 1-2
mucus glycoprotein
undegrated glycoprotein polymer
pepsin
degrated glycoprotein subunits

FIG. 14. Role of mucus and alkalisecretion in the protection of gastric mucosa against luminal acid and pepsin.

major role in the PG-induced gastric cytoprotection. Although the concept of unstirred layer of mucus and alkali may be a major factor in cytoprotection, further studies are required to elucidate the role of these factors in cytoprotection induced by PGs and other compounds.

Gastric mucosal microcirulation. Several studies showed that the mucosal ischemia may have a critical role in the genesis of ulcerations of mucosa exposed to damaging substances (81) and that the cytoprotective properties of PGs may be related to their effect on the mucosal microcirculation. Several PGs affect gastric vasculature and this occurs almost immediately after their administration. PGI_2, which is a potent vasodilator and a stimulant of the gastric mucosal blood flow, was reported to prevent the mucosal damage induced by indomethacin in rats (82) and by ethanol in dogs (83). It has been proposed that the increased gastric microcirculation may protect the mucosa by "sweeping away" excess of influxing H^+ and so preventing acidosis. Against this hypothesis is the fact that PG with opposite effects on gastrointestinal vascular beds are cytoprotective (1). Furthermore, the cytoprotective effect of PGs were demonstrated *in vitro* preparation where the blood supply is no longer intact (84).

Gastric mucosal barrier. PGs were reported to protect the gastric mucosal barrier against such damaging agents as ethanol, acidified aspirin or bile salts (83, 85, 86). On the other hand, 16,16-dimethyl-PGE_2 was reported to damage the gastric mucosal barrier when given into a Heidenhain pouch at higher concentration (87) or to remain without any influence on H^+ back-diffusion and to increase only the efflux of Na^+ into the gastric lumen when lower concentrations of PGE_2 were used (88, 89). The damaging effects of locally administered PGs could be simply explained by the local irritation of the mucosa by the high concentrations of PGs used in these studies (90).

Role of sodium and chloride pumps. Studies of Shanbour and her group (91–93) showed that 16,16-dimethyl-PGE_2 stimulates mucosal-to-serosal transport of sodium in the isolated canine gastric mucosa, whereas gastric damaging agents such as ethanol, aspirin or bile salts reversed this transport. It was suggested that the gastric sodium pump is essential for the integrity of mucosal epithelium and the cytoprotective effects of PGs have been attributed to their action on this pump.

Another study (94) *in vitro* frog gastric mucosa showed that acidified pepsin produced mucosal lesions when bicarbonate was removed from the nutrient bathing fluid. 16,16-dimethyl-PGE_2 inhibited lesion formation and stimulated chloride transport, indicating that cytoprotection may be causally associated with the activity of chloride pump in gastric epithelium.

Role of cyclic AMP formation. Some PGs are known to increase the cyclic AMP content of the gastric mucosa. Studies on the isolated mucosal cells demonstrated that this increase takes place in non-parietal cells originating from the surface epithelium (95). The rise in cyclic AMP was proposed as a possible mediator for cytoprotection because dibutyryl cyclic AMP and theophylline were shown to mimick the effects of PGE_2 on the sodium pump (96). Against this hypothesis is the fact that the dose of methylated PGE_2 required to elevate cyclic AMP in isolated non-parietal cells are supraphysiological. In addition, other PGs and other substances, for example, H_2-blockers are cytoprotective but they do not affect cyclic AMP accumulation in mucosal cells. It is more likely that different cytoprotective substances act via different mechanisms.

Role of Mucosal Growth and Protein Synthesis

The balance between cell loss and cell replication seems to be essential for the maintenance of the mucosal integrity. Agents which increase the rate of replication and cell maturation are likely to favor cytoprotection whereas factors which suppress cell replication and accelerate cell loss might increase the susceptibility to mucosal injury. Originally Robert (97) suggested that PGs may act as trophic hormones for the gastrointestinal mucosa and thus serve to maintain its integrity. This notion originated from observations that indomethacin causes severe lesions throughout the gastrointestinal mucosa and cytoprotective PGs are capable of reversing these effects. We confirmed that the suppression of mucosal cyclic-oxygenase by aspirin not only causes the formation of gastric lesions but also inhibits DNA synthesis. Exogenous PGs can prevent ulcer formation and the fall in DNA synthesis (68).

In patients with gastric ulcer, the loss of DNA into the gastric juice which reflects the rate of gastric epithelial cell shedding and serves as an index of mucosal integrity, was found to be markedly reduced by carbenoxolone (98). Since this drug accelerates the healing of peptic ulcer without affecting gastric secretion, it is possible that the cytoprotective action of this drug results, at least in part, from its growth promoting activity. More direct evidence for the role of mucosal growth in the cytoprotection was obtained by our group using epidermal growth factor (EGF) (68). This peptide which is known to stimulate the proliferation of epithelial cells lining the gastrointestinal tract, was found to exhibit cytoprotective properties. EGF prevented the formation of gastric mucosal lesions induced by aspirin and reversed the usual fall in the DNA synthesis in aspirin-treated gastric mucosa. It is possible that cytoprotective PGs and other cytoprotective substances increase the resistance of the gastric mucosa against various noxious agents predominantly by the prevention of the depression of the synthesis of DNA, RNA and protein and by promoting the growth of the gastrointestinal mucosa.

Against this concept is the observation that 16,16-dimethyl-PGE_2 is not a trophic agent for the gastric mucosal cells (99) and that the increase in the growth of the mucosa, even if it occurred, would require longer time than that during which cytoprotection appears.

Role of sulfhydryl substances. Gastric mucosa contains unusually high concentrations of nonprotein sulfhydryl compounds, particularly glutathione. The formation of ethanol-induced gastric lesions is preceded by a substantial fall in the sulfhydryl compounds, whereas sulfhydryl-containing drugs exert gastric cytoprotective effect comparable to that induced by PGs (100). Thus both exogenous and endogenous nonprotein sulfhydryls may provide gastric cytoprotection when present in the gastric mucosa in adequate amounts. The mechanism of this kind of cytoprotection is unknown but it may be due to binding of variety of electrophylic radicals and metabolites accumulating in gastric mucosa exposed to damaging agents. The concept of the mediation of the cytoprotection by endogenous sulfhydryls has been questioned because the reduction in gastric mucosal glutathione content caused by diethyl maleate also induced cytoprotection (101). It was proposed that the alteration in gastric mucosal content of glutathione modulates PG generation and that this contributes to the cytoprotection by agents affecting endogenous production of sulfhydryls.

Cytoprotection as physiologic phenomenon. Gastric cytoprotection induced by exogenous PGs and some gastrointestinal hormones actually occurs at relatively high doses and should be considered as a pharmacologic effect. The question remains whether PGs generated in the gastric mucosa are involved in maintaining cellular integrity of gastrointestinal mucosa. Various irritants present in the gastrointestinal tract such as spicy food, ethanol, bile salts, microorganisms etc. may stimulate the generation of PGs by mucosal cells and thus increase the resistance of the mucosa to the damage by strong irritants. Such "adaptive" cytoprotection has been demonstrated with regard to acidified bile salts, ethanol or hypertonic NaCl solution (1). It was accompanied by an increase in the capability of gastric mucosa to generate PGs (55) indicating that, indeed, locally generated PGs may be endogenous mediators involved in protective response to injury.

Besides PGs, some gastrointestinal hormonal peptides, particularly EGF and somatostatin, may contribute to the morphological and functional integrity of the gastric mucosa and this protection appears to be unrelated to the mucosal generation of PGs.

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Pharmacology and Clinical Use of Ranitidine

STANISŁAW J. KONTUREK, M.D.

Introduction

Although it is more than seventy-five years since histamine was first synthesized (1) and more than sixty years since the first realization that it is present in the gastric mucosa and stimulates gastric acid secretion (2), it was not until 1972 that it was fully established as a primary mediator of acid secretion (3). The work of Black et al (3) provided definite evidence for the existence of more than one type of histamine receptors. The concept that histamine receptors may be heterogenous was first suggested by Folkow et al (4) and then developed by Ash and Schild (5). They concluded that some effects of histamine such as contraction of intestinal smooth muscle and bronchial smooth muscle that can be blocked by mepyramine are mediated by H_1-receptors, whereas other effects are mepyramine-resistant and are mediated by H_2-receptors. Responses mediated through H_2-receptors include relaxation of contracted uterine smooth muscle, an increase in the frequency of contraction of cardiac muscle and secretion of gastric acid. Vascular smooth muscle appears to contain both H_1- and H_2-receptors, activation of both receptors subtypes causes vasodilation.

Elucidation of the histamine dual receptor hypothesis requires the identification of selective H_2 antagonists. This has been approached by Black's group (3) using similar experimental ways to those employed for the identification of adrenoreceptors (6), namely, comparison of the effects of natural mediator with those of a number of its close unnatural analogues in a range of pharmacological tests. The critical agonists were 2-methyl and 4-methyl histamine because of their selective actions on H_1- and H_2-receptors, respectively. The first series of discovered selective H_2 antagonists included substituted imidazoles: burimamide (3), metiamide (7), and cimetidine (8). Although all these drugs inhibited acid secretion, only cimetidine was applied successfully in the treatment of peptic ulcer disease. Burimamide was not found useful in medicine because of its weak activity and poor absorption from the alimentary tract, while metiamide caused a few cases of reversible agranulocytosis and was cancelled (9, 10). At present, cimetidine (Tagamet) is the most widely accepted representative of H_2 receptor antagonists, which in a number of well controlled clinical trials was found to speed the healing rate of duodenal ulcers (11) (Fig. 1).

The success of cimetidine in promoting the healing and preventing the recurrences of peptic ulcers is at present well documented but the drug has some limitations. Since it has a relatively low order of potency and is short-acting, a frequent dosing schedule is necessary. More importantly, its specificity of action is poor because it binds not only to H_2 receptors but also to other sites in the body and some of these interactions may give rise to clinically important side effects in some patients (12).

The best known additional binding sites are: 1) androgen receptors, the resultant antiandrogenic action leading to gynecomastia and sexual dysfunction in male patients (13, 14); 2) cytochrome P450, which is a part of the mixed function oxygenase enzyme system in the liver which metabolizes and inactivates many drugs such as propranolol, diazepam and warfarin, causing a marked potentiation and prolongation of their actions (15); 3) the uncharacterized binding sites in the brain resulting in mental confusion especially in the elderly (16); and 4) uncharacterized binding sites on peripheral blood lymphocytes which mediate their activation (17).

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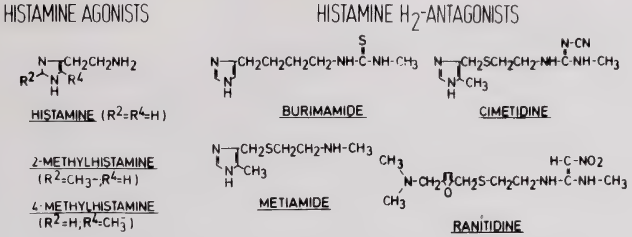

FIG. 1. Structure of histamine agonists and histamine H_2-receptor antagonists.

Chemistry and Pharmacology of Ranitidine

Classical H_2 receptor antagonists including metiamide and cimetidine, are imidazole derivatives like histamine itself. The basic imidazole ring present in their structure has been considered to be an important feature for activity and appropriate selectivity of action and potency have been achieved by varying the substituents carried on the ring.

In an attempt to obtain the drug with higher specificity to H_2-receptors and without unspecific binding at other sites in the body, an improved H_2-antagonist, ranitidine, was discovered by workers of Glaxo Research Group, England. Ranitidine is N[2[[[5-[(dimethyl-aminomethyl)]-2-furanyl]methyl]thio]ethyl]-N′-methyl-2-nitro-1,1-ethenediamine. It differs from cimetidine in being a substituted furan instead of an imidazole and in containing different ring substituents (18).

In experiments using isolated preparation such as guinea-pig isolated right atrium, guinea-pig isolated ileum, and perfused rat stomach, it has been shown that ranitidine is a selective and competitive histamine H_2-antagonist without any histamine H_1-antagonistic or anticholinergic activity. The potency of ranitidine as an H_2-antagonist was found to be 4–5 times greater than that of cimetidine (19).

The most important pattern of the action of ranitidine as H_2-blocker is a decrease in gastric acid secretion in response to various stimuli. *In vivo* studies on dogs with gastric fistulas and Heidenhain pouches, ranitidine was found to be 4.3 to 11.6 times more potent inhibitor of gastric acid secretion than cimetidine, antisecretory potency relative to cimetidine depending upon the type of gastric stimulation, the dose of the drug and the route of its administration. The most sensitive to ranitidine was meal-induced gastric secretion. The inhibition of gastric secretion by ranitidine was a consequence of direct action of the drug on the oxyntic glands as neither mucosal blood flow nor serum gastrin response was affected by the agent (19).

Since ranitidine is to be used clinically to aid healing rate of gastroduodenal ulcerations, the studies on animal models with peptic ulcerations were performed to investigate its antiulcer activity. Gastric ulcerations induced in cats by three hour infusion of aspirin and histamine or pentagastrin were decreased by ranitidine in a dose-dependent manner and this effect could be simply explained by the inhibition of gastric acid secretion by the drug (20). In another model utilizing aspirin-induced gastric ulcerations in rats, ranitidine prevented the formation of gastric lesions even in the presence of exogenous acid in the stomach (19, 21). The preventive action of ranitidine was not accompanied by any alteration of the generation

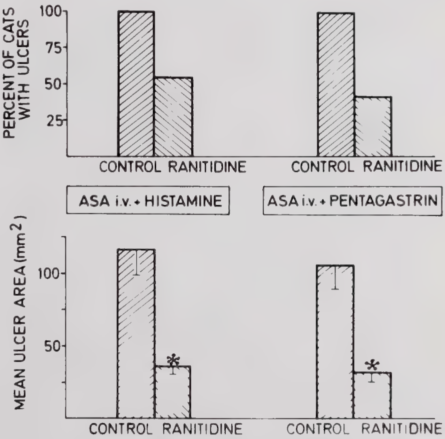

FIG. 2. Effects of ranitidine (40 μg/kg-h) on the rate of occurrence and the mean area of gastric ulcerations induced in cats by the combination of aspirin (60 mg/kg bolus injection + 20 mg/kg-h infusion) and histamine (80 μg/kg-h) or pentagastrin (8 μg/kg-h) given i.v. for 3 h in conscious cats (20).

of prostaglandins in oxyntic mucosa indicating that it is unrelated to endogenous prostaglandins and probably represents the property of the drug itself (21) (Fig. 2).

Unlike cimetidine which has relatively poor specificity of action and may cause several untoward side effects, ranitidine appears to be more specific. Long term toxicity studies with ranitidine have shown that this drug does not exhibit any antiandrogenic action and does not alter the mixed function oxygenase metabolizing enzyme in the liver and the drug metabolism (17, 22, 23).

Pharmacokinetics of Ranitidine

Ranitidine is well absorbed from the gastrointestinal tract in animals and is excreted mainly unchanged in the urine. Studies on ranitidine metabolism in dog and man showed that about 70%–80% of the administered dose is excreted in the urine (24). Renal clearance of ranitidine is several times higher (about 490 ml/min) than that of creatinine (125 ml/min) suggesting an active tubular transport of unchanged drug. Renal impairment may lead, therefore, to accumulation of ranitidine in the body and to the occurrence of drug toxicity. About 20%–30% of absorbed ranitidine is metabolized and the major metabolites excreted in the urine include the N-oxide, S-oxide and desmethyl of ranitidine. These metabolites are inactive except the last one but it constitutes only about 1% of the total dose (Fig. 3) (19, 24–26).

The bioavailability of ranitidine as determined from the comparison of the areas under the curve after intravenous and oral administration is about 50% (25, 26). The peak concentration of the drug after oral administration of various doses (20–100 mg) is achieved after about two hours and the plasma concentration which produced 50% inhibition of gastric acid secretion in man has been reported to be about 100 ng/ml (27). By contrast, similar inhibition by cimetidine requires an increase in the drug plasma level up to 500 ng/ml (28). After a single oral dose of 100 mg ranitidine plasma level of the drug above 100 ng/ml is maintained for longer than six hours. The concomitant intake of food with ranitidine does not change the overall bioavailability of the drug but shifts its peak plasma concentration by about 30–60 min towards the later time (Fig. 4) (25).

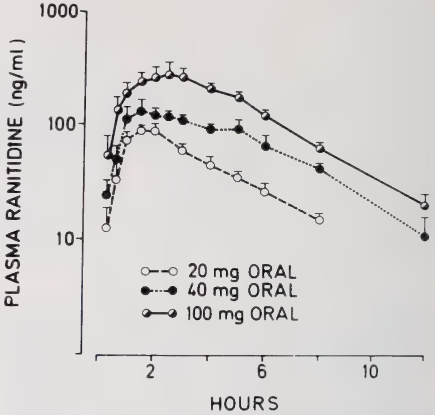

Fig. 4. Plasma concentrations of ranitidine after oral administration of its various doses.

Autoradiographic studies in the rat showed that radioactivity is distributed all over the tissues and can not be detected in the central nervous system or in the foetus of the pregnant animals. This indicates that central nervous side effects are unlikely to occur with ranitidine.

Inhibitory Effects of Ranitidine on Gastric Secretion in Humans. Dynamics of Gastric Inhibition

Ranitidine infused intravenously in graded doses against a constant background stimulation

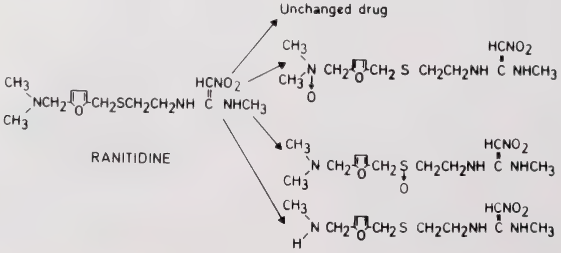

Fig. 3. Ranitidine and its major products of metabolism excreted in the urine.

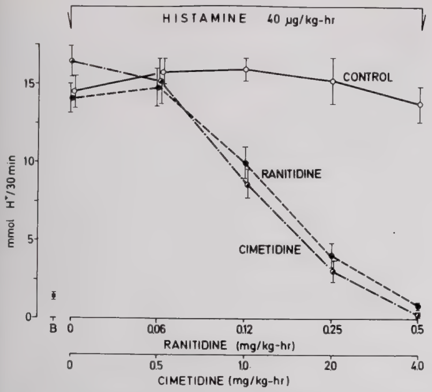

FIG. 5. Effect of ranitidine and cimetidine on histamine-induced gastric acid secretion in 8 duodenal ulcer patients (34).

with pentagastrin or histamine producing the highest observed acid response in duodenal ulcer patients caused a dose-dependent inhibition of acid and pepsin outputs. The dose of ranitidine producing 50% inhibition (ID_{50}) of pentagastrin-induced secretion was found to be about 0.125 mg/kg-h and this was about seven times smaller dose than that of cimetidine. In tests with histamine, the ID_{50} was 0.15 mg/kg-h and this was about ten times smaller than that of cimetidine (Figs. 5, 6) (29, 30).

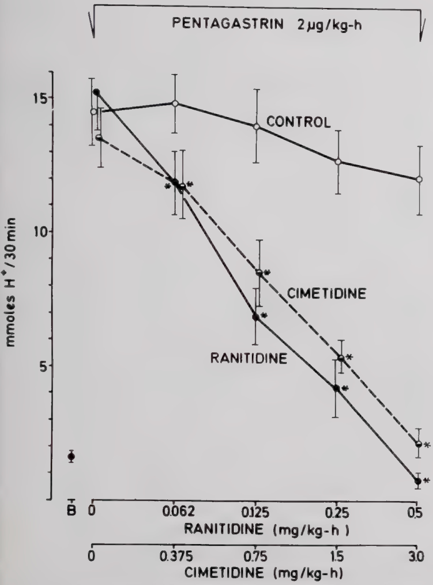

FIG. 6. Effect of ranitidine and cimetidine on pentagastrin-induced gastric acid secretion in 8 duodenal ulcer patients (31).

Pepsin secretion in tests with pentagastrin and histamine paralleled acid outputs and the reduction in pepsin outputs caused by ranitidine was mainly due to the decrease in the volume flow of gastric juice without significant change in pepsin concentration (31).

In studies on the dynamics of gastric acid inhibition, ranitidine was found to be a competitive inhibitor of histamine-stimulated acid secretion and a noncompetitive inhibitor of pentagastrin-stimulated secretion (Figs. 7, 8) (29, 30).

Ultrastructural studies on the resting oxyntic cells showed a large number of cytoplasmic tubovesicles and a small canalicular surface area. Following stimulation the number of tubovesicles was reduced and the canalicular surface area greatly increased. Soon after cessation of the stimulation the parietal cells proceeded back to the resting stage. In normal stomach, it is expected that the number of oxyntic cells in the stimulatory stage depends on the degree and the type of stimulation. Ranitidine appears to block the parietal cells in such a way that they cannot change from the resting to the active secreting stage. After prolonged treatment for one year, the oxyntic cells can still be inhibited; but 24 hours after the last dose, they respond to a meal with a usual ultrastructural changes characteristic of active acid secretion (Fig. 9) (32).

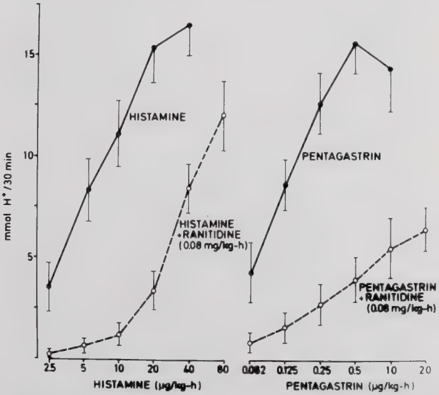

FIG. 7. Gastric acid outputs in response to pentagastrin alone or in combination with a constant dose of ranitidine (0.08 mg/kg-h) in 4 duodenal ulcer patients (30).

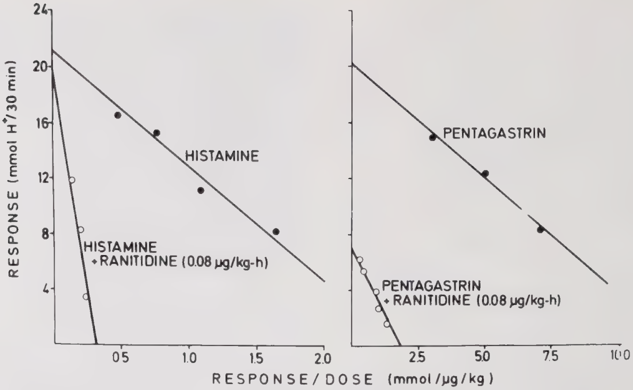

FIG. 8. Linear transformation of acid secretory data from Fig. 7. The intercepts of the regression lines on Y axis indicate the maximal calculated acid response and the slopes of the lines the D_{50} (30).

These observations remain in good agreement with secretory studies performed before and after short-term (four weeks) treatment with ranitidine in duodenal ulcer patients. It was found that neither basal nor maximally stimulated acid secretion was affected when the secretory tests were performed 48 hours after the last dose of the drug (31). Much effort was made to find out the potency of ranitidine in relation to cimetidine. In a dose-response studies on eight healthy volunteers using pentagastrin stimulation, it was found that ranitidine was more potent than cimetidine: 11 times with regard to volume, 13 times with regard to acid and nine times with regard to pepsin secretion (33). Comparison of equieffective concentrations in plasma resulted in a seven times greater potency of ranitidine than cimetidine (Fig. 10) (27).

Ranitidine also inhibited the secretory response to physiologic stimulation such as sham feeding and ordinary feeding. Stimulation by sham feeding resulted in acid output reaching about

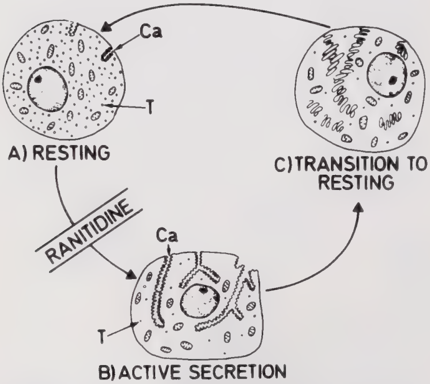

FIG. 9. The secretory cycle of the parietal cells. The resting parietal cells is characterized by numerous cytoplasmic tubulovesicles (T) and a few secretory cannaliculi (Ca) with microvilli. During active secretion (B) the tubulovesicles (T) are depleted at the expense of a great increase in the size of the secretory canaliculi (Ca). After acid secretion has ceased (C) the cannaliculi collapse, lose their microvilli and are thought to reform the numerous tubulovesicles of the resting cell. Ranitidine prevents the change of the cell from resting to active state (32).

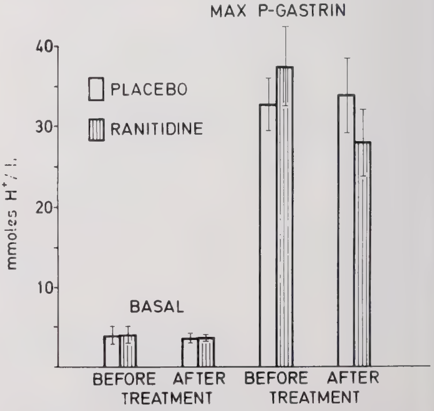

FIG. 10. Basal and pentagastrin-induced maximal acid outputs before and after treatment with placebo or ranitidine in 9 duodenal ulcer patients (31).

55%–65% of pentagastrin maximum. Ranitidine suppressed almost completely this response without affecting serum gastrin level and it was four to five times more than cimetidine in this respect (Fig. 11).

Acid response to a liver extract meal, introduced into the stomach to evoke the gastrointestinal phase of secretion, was almost as high as that to pentagastrin and accompanied by a marked rise in serum gastrin level. Both ranitidine and cimetidine greatly suppressed this secretory response without effecting serum gastrin levels, ranitidine being at least five times more potent inhibitor than cimetidine (Fig. 12) (34).

Effects of Orally Administered Ranitidine on Gastric Secretion. Possible Local Action of Ranitidine on Oxyntic Glands

Ranitidine given orally in various doses (range 20–80 mg) inhibited dose-dependently both basal and pentagastrin (2 μg/kg-h) stimulated gastric secretion. The inhibitory effects of oral 40 mg ranitidine on pentagastrin-induced secretion examined 4, 8 and 12 hours after drug administration were about 68%, 33% and 20%, respectively (31). Thus, a single oral dose ranitidine showed protracted inhibition of stimulated secretion up to about 12 hours. This corresponds with a prolonged elevation of plasma ranitidine after single oral dose of the drug (Fig. 13) (25).

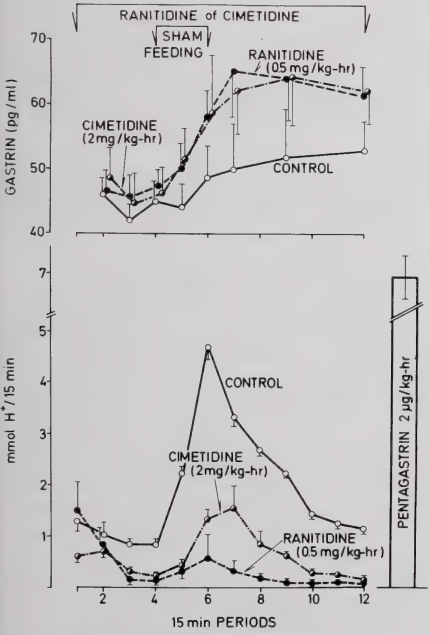

FIG. 11. Serum gastrin and gastric acid outputs in response to sham-feeding, with and without i.v. infusion of cimetidine or ranitidine in the some 8 duodenal ulcer patients. The column on the right indicate maximal pentagastrin-induced acid output.

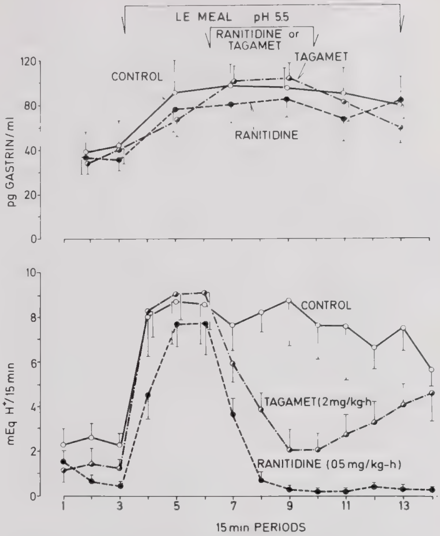

FIG. 12. Serum gastrin and gastrin acid responses to liver extract meal with and without i.v. infusion of cimetidine. Tagamet or ranitidine in duodenal ulcer patients (34).

In studies with 24 hour intragastric acidity and nocturnal acid secretion in patients with duodenal ulcer, ranitidine decreased acid secretion much stronger than cimetidine. Ranitidine in a dose of 150 mg given twice daily inhibited 24 hour intragastric acidity by 70% and nocturnal acid output by 90%, both aspects of acid secretion being significantly lower when compared in the same patients with cimetidine in standard dose, that is, 1 g in four daily portions. In this particular experimental model the molar ratio of cimetidine to ranitidine used was 4.2:1. The degree of acid inhibition achieved with four daily doses of cimetidine was comparable with that produced by a twice daily dose of ranitidine (35). Such twice daily medication has clear advantage in terms of patient compliance and convenience. On basis of this and previous studies the dose of ranitidine twice daily was recommended for the treatment of peptic ulcer disease (Fig. 14).

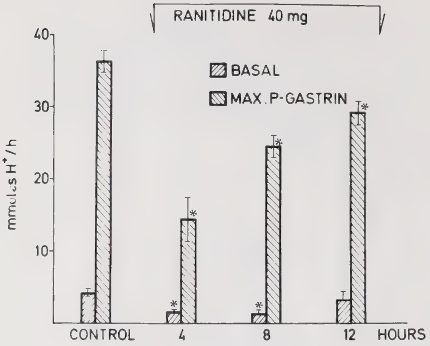

FIG. 13. Mean basal and peak acid response to pentagastrin 4, 8 and 12 h after oral administration of a single dose of ranitidine in 6 duodenal ulcer patients (31).

The inhibitory effect of oral ranitidine in humans appears to reach the maximum about two to three hours before the peak increase in plasma drug concentration (35). This suggests that ranitidine may have direct topical action on the oxyntic glands. We have tested this possibility by topical application of ranitidine to the Heidenhain pouch mucosa at the concentrations which may occur in the stomach after oral administration of the drug. This study showed that topical ranitidine, indeed, reduced significantly histamine-induced secretion and that this effect was not accompanied by any change in plasma ranitidine level. Thus, the evidence was provided that oral ranitidine have an inhibitory action at least in part due to its local effect on the oxyntic glands (Fig. 15).

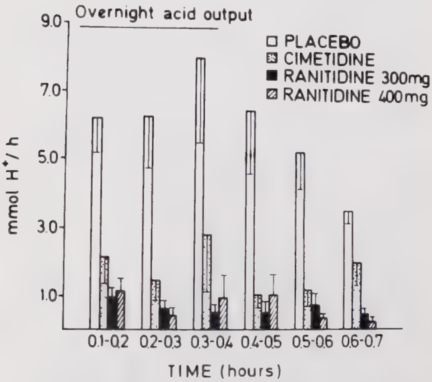

FIG. 14. Overnight acid outputs in duodenal ulcer patients after placebo, cimetidine in a standard dose of 1 g and ranitidine in a dose of 300 or 400 mg (35).

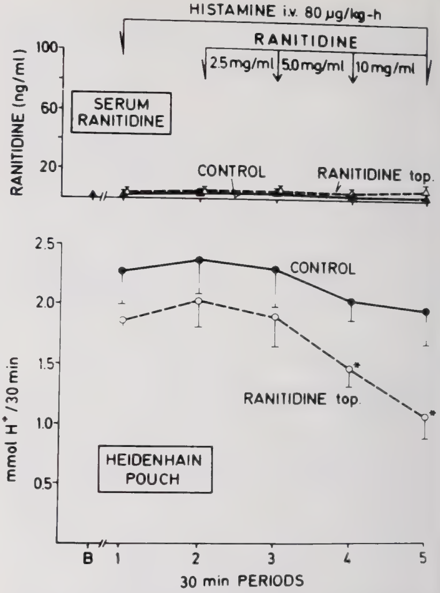

FIG. 15. Serum ranitidine level and acid secretion from the Heidenhain pouch in response to histamine stimulation with and without topical application of ranitidine in various doses (36).

Mechanism of the Inhibitory Action of Ranitidine on Gastric Acid Secretion

The findings that ranitidine inhibits gastric acid secretion induced by a variety of stimulants including histamine, pentagastrin, sham feeding, ordinary feeding and insulin (18, 21, 27, 29–31, 33, 35, 37, 38), indicate that histamine might be involved in the mediation of the secretory stimulants effect on the oxyntic glands. This points to the role of histamine as a primary mediator of gastric acid secretion, the concept suggested previously by McIntosh (39) and Code (40) who proposed that histamine is the "final common local chemostimulator" of the parietal cells, that is, all other secretagogues including gastrin and cholinergic stimuli excite the oxyntic cells via histamine (mediator hypothesis) (Fig. 16).

Several findings strongly argue in favor of the view that histamine plays a crucial role in the stimulation of gastric acid secretion. Histamine is

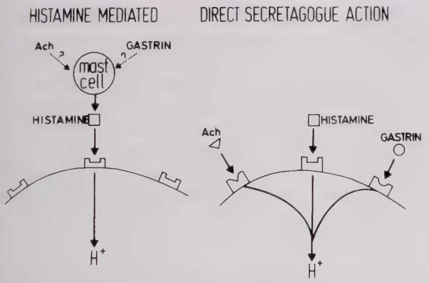

FIG. 16. Histamine mediator hypothesis and three receptor interaction concept of the stimulation of parietal cells (54).

formed and released from histaminocytes, specialized cells present in large number in the lamina propria of the oxyntic mucosa and preferentially situated in the proximity of the oxyntic cells (41–43). Oxyntic mucosa contains histidine decarboxylase which catalyzes the formation of histamine from histidine; the activity of this enzyme increases in response to feeding and vagal stimulation which are known to release gastrin and acetylcholine in the gastric mucosa (44, 45). Hormonal inhibitors such as secretin or somatostatin fail to affect the mobilization of gastric histamine or the activation of histidine decarboxylase and these substances also fail to influence histamine-induced gastric secretion (47, 48). Finally, histamine is the most potent stimulant of the isolated parietal cells or isolated oxyntic glands as evidenced by an increase in oxygen uptake, adenyl cyclase activity, aminopyrine uptake and cyclic AMP accumulation (49). Histamine interacts also with other stimuli resulting in a markedly potentiated effect (50). The receptors mediating histamine stimulation of the oxyntic cells have been characterized pharmacologically as H_2-receptors (3) and identified in the oxyntic cell membrane using ^{14}C-histamine binding procedure (51).

In terms of physiologic control of gastric acid secretion the complementary roles of vagus and gastrin are well established (52). Vagal stimulation or the presence of food in the stomach provokes the release of gastrin from the G-cells of gastric antrum and the secretion of acid. Both these effects are inhibited by atropine, which block muscarinic cholinergic receptors and by ganglion-blockers, which block nicotinic cholinergic receptors. The same drugs inhibit also acid secretion induced by exogenous gastrin and cholinergic stimuli but little influence histamine-induced secretion (53). As shown on the model proposed on Fig. 17, this interrelationship could be explained since histamine is the primary mediator of gastric acid secretion during cephalic and gastric phase of secretion.

It is unknown, however, how the release of histamine is stimulated during these phases. The histaminocytes seem to be activated by acetylcholine released from the neurons of the intramural nerve plexus, and acting via receptors of the muscarinic type. In addition, oxyntic cells seem to be also excited directly by acetylcholine released from the postganglionic neurons. This is supported by the fact that cholinergic stimulants activate the isolated oxyntic cells and that this activation can be abolished by anticholinergic but not by histamine H_2-blockers (50). Gastrin was also reported to stimulate oxyntic cells. These observations indicate the existence of oxyntic cell receptors not only for histamine but also for acetylcholine and gastrin, each directly stimulating the oxyntic cells and resulting in potentiating interaction between secretagogues (50). It was initially hypothesized that these interactions may result from positive cooperation between the receptors for these secretagogues but now another explanation seems more likely. Based on studies on the isolated oxyntic cells, it has been suggested that histamine may be constantly released from the mucosa and may sensitize the parietal cells to other stimuli such as gastrin and acetylcholine (permissive hypothesis) (54).

Effect of Ranitidine on Gastroduodenal and Pancreatic Alkaline Secretion

The presence of bicarbonate in gastric and duodenal secretions has been reported in laboratory animals and humans but only recently has it

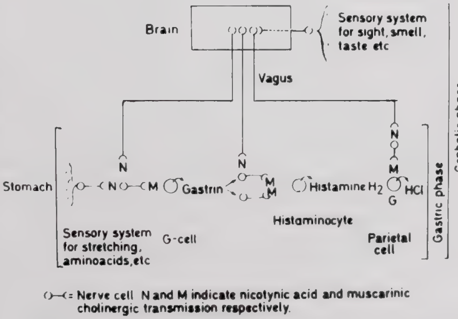
Brain
Sensory system for sight, smell, taste etc
Vagus
Cephalic phase
Stomach
N
N
N
M
M
M
M
Gastrin
Histamine H2
G
HCl
Histaminocyte
Gastric phase
Sensory system for stretching, aminoacids, etc
G-cell
Parietal cell
O—<= Nerve cell N and M indicate nicotynic acid and muscarinic cholinergic transmission respectively.

FIG. 17. Role of histamine in the stimulation of gastric acid secretion during cephalic and gastric phases.

been attributed to the active transport (55, 56). This alkaline secretion has been suggested to play an important role in protecting the gastric epithelium from damage by various irritants (57, 58). Accordingly, several potential ulcerogens such as antiinflammatory drugs were found to inhibit alkaline secretion (59), whereas some prostaglandins with known antiulcer activity were found to increase this secretion (59, 60).

The effects of ranitidine on alkaline secretion were not examined, but other H_2-blockers were reported to be without any influence on this secretion (61). We have performed experiments in conscious dogs provided with separate fundic, antral and duodenal bulb pouches (Fig. 18). Secretion of acid from the fundic pouch was blocked by topical application of 16,16-dimethyl PGE_2. Bicarbonate secretion was measured by back-titration with acid solution of the fluid bathing the pouch mucosa to its original pH 5.0. Under these conditions, the alkaline secretion was well sustained throughout the study, the duodenal mucosa secreting two to three times more bicarbonate than fundic or antral mucosa. Ranitidine, given i.v. in a dose (0.5 mg/kg-h) that caused almost complete inhibition of histamine-induced acid secretion, did not affect alkaline secretion in fundic, antral or duodenal mucosa. These studies indicate that protective effects of ranitidine against mucosal injury is unlikely to result from increased alkaline secretion (21). Obviously this secretion does not seem to contribute to the reduction in acid output observed after ranitidine administration.

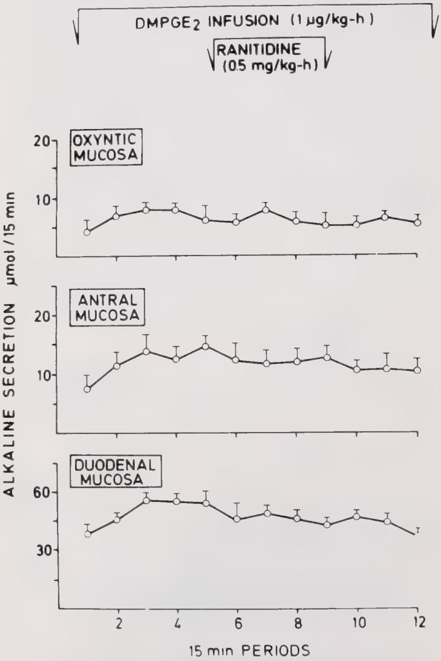

FIG. 18. Effect of ranitidine given i.v. on alkali secretion induced by 16,16-dimethyl PGE_2 given i.v. from Heidenhain pouch, antral pouch and duodenal pouch in dogs.

The effects of ranitidine on pancreatic bicarbonate secretion was determined in eight duodenal ulcer patients receiving i.v. infusion of secretin (1 U/kg-h plus CCK 1 U/kg-h). When pancreatic secretion reached a plateau induced by infusion of secretin plus CCK, ranitidine (0.5 mg/kg-h) was added to infusion (31). No significant changes in the pancreatic volume flow, bicarbonate or enzyme outputs were observed. Thus, ranitidine, like cimetidine (62) was found to be without any influence on pancreatic secretion (Fig. 19) (31).

Effect of Ranitidine on Gastric Mucosal Blood Flow

Studies on experimental animals showed that the blockade of H_2-receptors does not affect resting mucosal blood flow but reduced the blood flow during histamine-induced secretion probably due to the decrease in the gastric acid secretion caused by this blockade (63). It has been suggested the histamine H_2-receptors are implicated in the control of gastric acid secretion and the com-

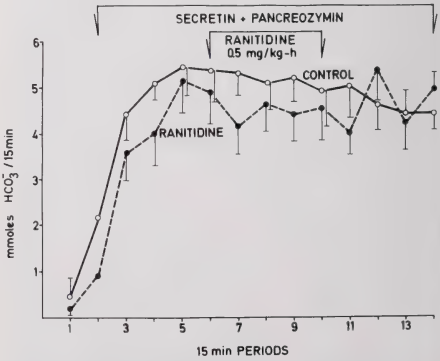

FIG. 19. Effect of ranitidine given i.v. on pancreatic bicarbonate secretion induced by secretin + pancreozymin in 8 duodenal ulcer patients (31).

bination of H_1- and H_2-receptors is involved in the control of gastric vasculature (64).

Studies on healthy volunteers using neutral red clearance (NRC) technique showed linear relationship between NRC and acid outputs induced by pentagastrin or histamine (65). Ranitidine or cimetidine caused a parallel dose-dependent displacement of both curves to the right, however, the effect on the blood flow was relatively less pronounced than that on acid secretion (66).

We performed studies using ^{14}C-aminopyrine clearance technique in six duodenal ulcer patients during i.v. infusion of graded doses of pentagastrin (0.062–2.0 μg/kg-h) with and without addition of ranitidine (0.08 mg/kg-h). Ranitidine decreased both acid secretion and mucosal blood flow in an usual noncompetitive manner. As in previous studies on healthy subjects (66), the reduction in acid response was greater than that in gastric vasculature (Fig. 20). This suggests that H_2-blockade normalizes the ratio of the gastric acid secretion to gastric mucosal blood flow which may be disturbed in the duodenal ulcer.

Clinical Use of Ranitidine

The original reason for the development of the H_2-receptor antagonists was an attempt to produce drugs which would block the H_2-action of histamine and reduce acid secretion to the extent favoring the healing rate of peptic ulcerations. The large number of clinical trials performed in various centers all over the world indicate the very great interest in the clinical application of H_2-receptor antagonists to the treatment of duodenal ulcer. The effectiveness of the drug was determined in the short-term treatment lasting up to 12 weeks, and in the maintenance therapy intended to prevent relapses for a period of six months or longer. In most trials with cimetidine, a significantly higher percentage of duodenal ulcers was healed than placebo, both groups of patients receiving ad lib supplies of antacid (67–72). In some trials cimetidine was, however, reported to be no better than either placebo or intensive antacid therapy (73, 74).

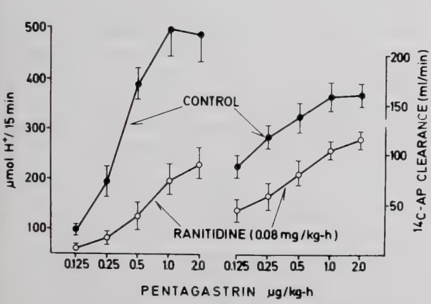

FIG. 20. Gastric acid secretion and ^{14}C-aminopyrine clearance in response to graded doses of pentagastrin with and without ranitidine in 6 duodenal ulcer patients.

Clinical trials utilizing the greater potency of ranitidine have compared a twice daily regime of this drug with the conventional four times daily administration of cimetidine in a total daily dose of 1 g. Results showed that in the short-term, ranitidine was as effective as cimetidine, and superior than placebo in the treatment of duodenal ulcer (75, 76, 77).

The maintenance trial of duodenal ulcer with cimetidine 400 mg at night or 400 mg twice daily show a significant advantage of this drug over placebo. After six months of maintenance therapy, approximately 85% of duodenal ulcer patients remained in remission, contrasting with only 40% of these receiving placebo. The annual recurrence rate of duodenal ulcers on long-term treatment was approximately 23% compared with 100% on placebo (78, 79).

On-going maintenance trials of duodenal ulcer with 150 mg ranitidine taken with the evening meal, showed that the annual rate of symptomatic recurrences in patients receiving ranitidine was 14.3%. This value was significantly better than the cumulative annual symptomatic release rate of 19.4% reported for multicenter data using cimetidine 400 mg nocte in the maintenance therapy (80, 81).

The major difference in the treatment between cimetidine and ranitidine is the drug tolerance and adverse effects, which were reported in trials with cimetidine but not with ranitidine. The major side effects reported for cimetidine include antiandrogenic activity with gynecomastia and sexual dysfunction, inhibition of the oxidative metabolism of other drugs with potential drug toxicity, stimulation of the prolactin release and the effects on the central nervous system with mental confusion observed particularly in elderly patients (12–17). None of these side effects was linked with H_2-receptor blockade and they did not occur during short-term treatment or in maintenance therapy of ranitidine (17). Both cimetidine and ranitidine therapy can lead to bacterial colonization of the stomach but it is unknown whether this may have clinical consequences or generate carcinogenic nitrosamines or nitrosamides (83). Extensive toxicologic studies in animals carried out with ranitidine including life span carcinogenicity tests in the mouse and rat have shown no adverse effects of significance to its use in man (72).

Ranitidine, like cimetidine, has been attempted in the treatment of other acid-pepsin disorders such as gastric ulcer, reflux esophagitis, stress ulceration in seriously ill patients, upper gastrointestinal bleeding, and gastroduodenal ulcerations associated with Zollinger-Ellison syndrome (72, 85). In most reports, the effects of ranitidine were comparable to those of cimetidine. Some Zollinger-Ellison syndrome peptic ulcerations who become resistant to the treatment with cimetidine or developed untoward effect of cimetidine improved after replacement of cimetidine by ranitidine treatment (84).

In all patients, the treatment with ranitidine was well tolerated and no significant adverse effects have been recorded.

These data appear to indicate that ranitidine is a safe and effective compound for use in short-term and maintenance therapy of duodenal ulcer and other acid-pepsin disorders. In view of the prompt symptomatic release which occurs on withdrawal of ranitidine after one year of maintenance treatment for duodenal ulcer, administration of ranitidine should be continued for longer although the optimum duration of therapy remains to be determined (80).

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The Inadequate Evidence for Short Hospital Stay after Hernia or Varicose Vein Stripping Surgery

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Introduction

Traditionally, decisions made about the appropriate treatment of patients with a given disorder have been made by clinical experience modified by the evaluation of the scientific literature. Results reported in reputable journals by well-established physicians are given more credence. However, there is ample evidence in medicine that an agreed upon *optimal* treatment based on both clinical experience and the literature has been shown to be less than optimal by randomized control trials. In addition, there are many examples in the literature in which there exists no "agreed upon" optimal treatment. In these situations, there can be as many conflicting opinions on the choice of a treatment as there are authors. Examples of medical areas in which this situation occurs are in the use of anticoagulants in myocardial infarction, the use of oral hypoglycemics in the treatment of diabetes, the use of alternative drugs in the treatment of duodenal ulcer, and the use of portal caval shunt operations in liver disease.

More and more the use of the randomized control trial (RCT) to evaluate alternative therapies or treatment regimens is becoming the research methodology of choice (1). However, just as the reliability of clinical experience and the general medical literature has been shown to be less than perfect, the same can be said of published articles on RCT's. Several articles have appeared pointing out these inadequacies and calling for the establishment of standards for the conduct and reporting of RCT's (1). Chalmers et al (2), have developed a technique for quantitatively evaluating the reported results of a RCT. These new papers enable an investigator to evaluate controversial alternative therapies in an objective manner.

In this paper, we consider the controversy over long or short hospital stay following surgery for hernias and for varicose vein stripping. There are approximately 533,000 hernia operations performed in the United States each year. The average hospital stay following the hernia operation is from five to seven days at a cost of approximately $300 per patient per day. It is important to know whether or not a shorter postoperative hospital stay is a viable alternative; that is, when a reduction in total cost (in and out of hospital) could be obtained without additional risk to the patient's health.

Materials and Methods

A computerized English literature search was conducted for randomized control trials comparing long and short hospital stay following hernia or varicose vein stripping surgery. During the years 1960–1979, six trials involving hernias (3–10) and four trials involving varicose vein stripping (3, 6, 9, 10) were found.

The quantitative method used in this paper involves grading each clinical trial on three major components: protocol design and planning, statistical analysis, and presentation of results. In doing the grading, unbiased evaluators are required. To help insure no evaluation bias, the methods section of each paper is reproduced obliterating the end results, author, and title of the journal. Three evaluators grade each paper and a final consensus score is obtained.

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Form 1 included descriptive, nonevaluable data.

Form 2 was used in grading the protocol design and planning elements of each paper. The important elements to be scored were the blinding of randomization, physicians, and patients; the description of patient selection; prior estimate of number of patients required; presence of a reject log; the description of therapeutic regimens, and the testing of randomization. Several items were considered nonapplicable: control regimen appearance and taste, testing compliance (since everyone complies with a surgical procedure and once released from the hospital are necessarily complying to the predetermined length of stay), biological equivalent which refers to measuring a drug effect biologically—clearly not an issue in these surgical trials, and blinding of patients. Testing of blinding was applicable only on trials that had blinded the physicians.

Form 3 was used to evaluate the statistical analysis. Points were given for the inclusion of such items as statistical tests of hypothesis, confidence interval statements, investigations of issues involving sources of nonrandom error, and statistical discussion of retrospective analyses and side effects. Life table or actuarial curves and regression analysis were considered nonapplicable. In addition, the statistical discussion of side effects was not applicable because any incident following surgery was considered a complication and treated as an end point.

Form 4 was used to assess the reporting of endpoints.

Final quality scores for each component and for the overall trial were obtained by dividing the number of points obtained by the total number of possible points—a batting average type statistic. The total number of possible points was obtained after the exclusion of non-applicable items.

Certain results were pooled across all studies to investigate whether any nonstatistically significant trends in individual papers became significant when results were combined. The Mantel-Haenszel (11) procedure was used to test hypotheses on the combined data.

Results

A. Analysis of Overall Quality

The quality assessment scores for both the protocol (Form 2) and statistical analysis (Form 3) as well as the overall quality for these papers are shown in Table I. The average score for the protocol and planning section as $\bar{X} = .347$ with a standard deviation of $s = .181$. The average quality score for the statistical analysis sections was $\bar{X} = .373$ with a standard deviation of $s = .131$. The average overall quality score was $\bar{X} = .349$ with individual scores ranging from .204 to .494.

TABLE I

Quality Scores

Paper #	Form 2	Form 3	From 4	Total
(Same 9, 10 11 trial)	.225	.476	.400	.319
12	.263	.500	.600	.387
13	.663	.348	.000	.480
14	.250	.130	.200	.210
15	.160	.304	.200	.204
16	.520	.478	.400	.494
Average	.347	.373	.300	.349
Standard Deviation	.181	.131	.191	.116

The aspects of the trials which affected the quality scores of the trials are shown in Table II. The number of papers receiving some credit for the methodologic criteria are shown in the positive column. Those positive aspects were the selection of patients descriptions, the use of patient reject log, the carefully recording of withdrawals with reasons for withdrawal, the description of therapeutic regimens and the testing of randomization. The negative aspects which tend to lower quality scores included the lack of blind-

TABLE II

Characteristics of the Six Trials

	Number of Studies		
Methodologic Criteria	Positive*	Negative*	Unknown
Selection description	6	—	—
Reject Log	4	2	—
Withdrawal list	6	—	—
Therapeutic Regimens	6	—	—
Blinding of:			
Randomization	2	—	4
Physicians (re therapy)	2	3	1
Physicians (re results)	—	1	5
Patients	—	—	—
Prior estimate of numbers	—	6	—
Testing randomization	4	2	—
Statistics:			
General analysis	2	4	—
Test statistic	5	1	—
Confidence limits	—	6	—
Posterior estimates of numbers required	—	6	—
Retrospective analysis	1	5	—
Blinding statistician (re results)	—	—	6

* Positive—indicates the paper either had the characteristic or scored some points for approaching the quality requirement.

* Negative—indicates the paper did not have the characteristic and did not score points.

ing of randomization, physicians, and statisticians; poor statistical analysis and no evidence of valid procedures for estimating appropriate sample sizes prior to the start of any trial. The failure of any of these papers to determine the proper sample size prior to doing the trial becomes most worrisome when looked at in relation to a particular finding of these papers; for example, when the trials show no statistically significant difference between the complication rates resulting from short and long term hospital stay (12). With small sample sizes it is very easy to show no statistically significant differences, particularly when both the rates being compared and the differences of interest are small.

B. Comparison of Hernia Repair Trials with Vein Stripping Trials

Quality Scores

A comparison of total quality of the two types of surgical trials showed no statistically significant difference ($p > .05$) in quality scores between papers investigating length of hospital stay for varicose vein patients and those investigating length of hospital stay for hernia patients. However, both scores are very poor; i.e., .407 and .367; respectively and the number of trials is small. A 95% confidence limit on the true difference in quality scores was $-.133$ to .214 or $-.133 \leftrightarrow .213$.

Endpoints (Outcomes)

Three major endpoints were investigated: Complications, length of convalescence (days), costs. In one hernia trial, recurrence of hernias were also reported, but are not shown in this paper. Table III shows the nonuniformity of endpoint reporting and average sample size, n, for these trials.

Inspection of Table III indicates the difficulty coming to any overall conclusion about long and short stay in these trials. The sizing is small and highly variable, and the reporting is far from uniform.

The specific quantifiable results for these trials are shown in Tables IV and V.

The results in Table IV can be summarized as follows:

Hernia

There were no statistically significant differences (that is, $p > .05$) and no trends of interest in complication rates or length of convalescence between long and short hospital stay. As to cost, only one trial (3–5) adequately measured overall costs and in this trial there was a trend for lower costs with short stay but this did not reach $\alpha = .05$ the statistical significance level. Obviously hospital costs (only) are markedly less for short stay.

Varicose Vein Stripping

In one trial (3, 4, 5) there was a significant increase ($X^2 = 7.89$, $p = .005$) in varicose vein stripping complications with the short stay group with the tendency repeating in one other trial (9). The third reporting trial (10) had only a total of $n = 6$ patients. No difference in average convalescence days was shown, and the same results on costs shown for hernias apply here.

Combining Trial Results

Since all the reported trials had small sample sizes, it would be helpful if an estimate of the differences between long and short stay could be obtained using all the data. Using data from

TABLE III

Frequency of Endpoint Reporting

	Hernia				Varicose Veins			
Trial #	Av** n	Complications	Convalescence	Cost	Av. n	Complications	Convalescence	Cost
9								
10, 11	52	✓	✓	✓	58	✓	✓	✓
12	93	✓				////	////	////
13	38*	✓†		✓	142	✓		✓
14	56*	✓	✓	✓		////	////	////
15	14*	✓			12	✓		
16	19	✓	✓	✓	3	✓	✓	✓

//// Varicose Veins not included in trial.

** AVG. # of Pts on long and short stay groups

* Sample sizes grossly unbalanced between long and short stay.

† Complications reported but not analyzed separately by type of surgery.

TABLE IV

Complication Rates, Average Number of Convalescence Days, and Average Costs ($ or £) in Hernia and Varicose Vein Trials

Type	Paper Number	Hernia		Varicose Veins	
		Short Stay	Long Stay	Short Stay	Long Stay
Complications					
(rates)	3,4,5	7/56(12.5)	5/49(10.2)	8/61(13.1)	0/56/(0)
	6	25/92(27.2)	18/93(19.4)		
	8	12/32(37.5)	28/79(35.4)		
	9	0/9 (0)	2/19(10.5)	6/15(40)	2/10(20)
	10	1/19(5.3)	1/19(5.3)	0/3 (0)	0/3 (0)
Convalescence					
(Av. No. of Days)	3,4,5	38.2	34.5	21.8	21.3
	8	14.67	12.5		
	10	13.7	22.9	25.0	26.7
Costs					
(Av. $ or £s)	3,4,5	$324.34	331.24	145.45	165.07
	7*	X − 100	X	X − 100	X
	8*	X − 33	X		
(hospital only)	10	$85.90	$362.50	$68.84	$446.63

* Costs show short stay to be 100£ less per day than long stay for trial #7 and 33£ less for trial #8.

Table III, the complication rates from all but trial 7 were combined and are shown in Table V.

From Table V, we get the same results as before; that is, no significant difference in complication rates between long and short stay for hernias, and significant ($Z = 2.52$, $p = .01$) differences (short stay with more complications) for varicose vein stripping.

Assessment of the Size of Reported Trials

In Table V, an estimate of the overall crude complication rate for hernias with a short hospital stay was 22% and with varicose veins 18%. An indication of the kind of sizing that would be required for trials with an average complication rate of 20% and a requirement of being able to detect a reduction of X% in the long stay complication rate compared to the short stay with $\alpha = 5\%$ and $\beta = 10\%$, is shown in Table VI (13).

All trials in these papers were too small. At least 125 on both short stay and long stay are needed to show a 15% reduction in complication rates with $\alpha = 5\%$, $\beta = 10\%$.

TABLE V

Total Combined Results on Complications for both Hernia and Varicose Vein Trials

Statistics	Hernia	Varicose Veins
Mean Sample Size (n): Short Stay	41.6	26.3
Mean Sample Size (n): Long Stay	51.8	23.0
Mean Sample Size (n): Combined	46.7	24.7
Crude Complication Rate: Short Stay	.216	.177
Crude Complication Rate: Long Stay	.208	.029
Difference (Short Rate—Long Rate)	.008	.148
X^2 (Combined Complication Results)*	.754	6.33
Z (Combined Complication Results)*	.869	2.52

* Results Combined Using Mantel-Haenszel Procedure (11)

Authors Recommendations

Table VII summarizes the decisions made in the papers by the respective authors.

Conclusions

None of these reported trials meet present day standards for quality. A good trial should score in the .900 range—none of these trials score above .550. In all likelihood, the lack of significant differences in the results can be attributed to inadequate sample sizing. The lack of sufficient information on overall costs in these trials make the universal conclusion in favor of short hospital stay very tenuous. In the one trial (quality score only .392) when a real attempt was made to measure overall costs, the result while favoring short stay did not reach the $\alpha = .05$ level of significance.

Discussion

The universal conclusion of all authors (Table VII) to recommend short hospital stay based mainly on costs should be regarded with caution.

TABLE VI

Total Number of Patients in a Trial for Detecting X% Differences in Complication Rates ($\alpha = 5\%$, $\beta = 10\%$)

Short Stay	Long Stay	Δ	Total n
20%	15%	5%	2132
20%	10%	10%	832
20%	5%	15%	250

TABLE VII

Decisions Reported in the Trials Based on the Three Major Endpoints

Paper	Surgery Type	Trial Quality Score	Decision on Convalescence	Decision on Complications	Decision on Costs	Decision on Procedure
3,4,5	Hernia		ND	ND	ND	USS
	Varicose Veins	.392	ND	SSM	ND	USS
6	Hernia	.382		ND		USS
7	Hernia			NS	SSL	USS
	Varicose Veins	.506		NS	SSL	USS
8	Hernia	.190	ND	ND	SSL	USS
9	Hernia			ND		USS
	Varicose Veins	.232.		ND		USS
10	Hernia		SSL	ND	SSL	USS
	Varicose Veins	.499	SSL	ND	SSL	USS

ND = No Difference
SSL = Short Stay Less
SSM = Short Stay More
NS = Not Stated
USS = Use Short Stay

The variability between trials on which variables influencing cost were investigated was tremendous. In the only United States (U.S.) publication (10), hospital costs were reported with no mention of potential outside ancillary costs to the short stay group. These might include loss of work, loss of wife's/husband's work, private duty nurses, and increasing visits to private physicians, to mention just a few. Only one paper by Adler (3–5) investigated the cost issue thoroughly enough to warrant confidence in the results. Interestingly, this is the one paper which found no significant difference in costs between short and long stay after surgery. Further, despite this conclusion, his decision was that short stay should be used. Adler has subsequently published another paper (14) that reports how styles in terms of lengths of hospital stay after varicose vein stripping and hernia repair are changing to decrease stay in England.

Recently, Nabatoff (15) and others, have reported experiences with ambulatory patients in the U.S., indicating the trend to use shorter stays in this country. This development has taken place even when there is very little hard evidence that short stay is cost effective and not more risky to the patient. Undoubtedly, the shorter stay decision has been made because of two factors: 1) the good experiences surgeons are having with individual cases, and 2) the obvious low cost of short hospitalizations. However, the caveat presented in the introduction must be kept in mind. Without good clinical evidence, what is superficially perceived to be true about a treatment may not actually be true when the question is adequately studied.

Costs have *not* been adequately studied, and it may be that releasing patients from the hospital early after one of these procedures may burden other services and cost more.

The complication results deserve some discussion. The conclusion that there is no difference in complication rates following a hernia repair whether patients stay a long or short time in the hospital is based on papers generally rated poor. If one feels the quality to be sufficiently poor as to disregard all results, then no general decision in favor of short stay should be made. If, on the other hand, one believes that despite the poor overall quality of the trials, one can use the results, then one concludes that complication rates may not differ but that the cost is an issue that should be further investigated.

Form 2: The Study Protocol

ID # ______________________________ Study # ______________________

2.1 Selection description:
- ___1. Adequate
- ___2. Fair
- ___3. Inadequate

2.2 Number of patients seen and reject log:
- ___1. Yes
- ___2. Partial
- ___3. No
- ___4. Unknown

2.3 Withdrawals:
___1. List given
___2. No withdrawals
___3. No list
___4. Unknown
___5. >15% withdrawals for long-term studies and >10% for studies lasting less than 3 months

2.4 Therapeutic regimens Definition:
___1. Adequate
___2. Fair
___3. Inadequate

2.5
A. Control regimen (placebo) appearance:
___1. Same
___2. Different
___3. Unstated
___4. N.A.

B. Control regimen (placebo) taste:
___1. Same
___2. Different
___3. Unstated
___4. N.A.

2.6 Randomization blinding:*
___1. Yes
___2. Partial
___3. No
___4. Unknown

Method of random blinding
___1. Envelope
___2. Pharmacy
___3. Other
___4. Unknown
___5. N.A.

2.7 Blinding of patients:*
___1. Yes
___2. No
___3. Unknown
___4. N.A.

2.8 Blinding of physicians re therapy
___1. Yes
___2. Partial
___3. No
___4. Unknown
___5. N.A.

2.9 Blinding of physicians and patients re results:*
___1. Yes
___2. Partial
___3. No
___4. Unknown

2.10 Prior estimate of numbers: (endpoints selected, diff. of clin interest α & β estimated)
___1. Yes
___2. No
___3. Unknown

2.11 Testing randomization:
___1. Yes
___2. Partial
___3. No
___4. Unknown

2.12 Test blinding:
___1. Yes
___2. Partial
___3. No
___4. Unknown
___5. N.A.

2.13 Testing compliance:
___1. Yes
___2. Partial
___3. No
___4. Unknown
___5. N.A.

2.14 Biological equivalent:
___1. Yes
___2. No
___3. Unknown
___4. N.A.

* See Table I for explanation of multiple possible scoring.

Form 3: Statistical Analysis

ID # ______________ Study # ______________ Reader: ______________

3.1 On major endpoints:
___1. If possible statistic and observed probability value are stated
___2. If observed probability level given, but test statistic value not stated
___3. If test statistic, but not observed probability value given
___4. If neither test statistic nor observed probability level given

3.2 Posterior β estimate of observed diff. for negative trials:
___1. Yes
___2. Mentioned and necessity for more patients
___3. No
___4. N.A.

3.3 Statistical inference:
A. Confidence limits:
___1. Yes
___2. No
___3. N.A.
B. Life table or time series analysis:
___1. Yes
___2. Shown but incorrect
___3. No
___4. N.A.
C. Regression analysis correlation:
___1. Yes
___2. No
___3. N.A.

3.4 Appropriate statistical analysis
___1. Excellent
___2. Good
___3. Poor
___4. Inadequate

3.5 Handling of withdrawals:
___1. Analyzed several ways
___2. Included in original rand.
___3. Discarded
___4. Changed groups
___5. Unknown
___6. No withdrawals—N.A.

3.6 Side effects—statistical discussion:
___1. Adequate
___2. Fair
___3. Poor
___4. N.A.

3.7 Proper retrospective analysis:
___1. Good
___2. Partial
___3. None

3.8 Blinding of statistician or analyst re results:
___1. Yes
___2. No
___3. Unknown
___4. N.A.

3.9 Multiple looks considered:
___1. Yes
___2. Fixed sample size—no look
___3. No

Form 4: Presentation of Results

ID # ______________ Study # ______________ Reader: ______________

4.1 Dates of starting and ending accession:
___1. Yes
___2. No

4.2 Results of prerandomization:
A. Data Analysis:
___1. Adequate
___2. Fair
___3. Inadequate
B. Prognostically favoring:
___1. Treatment
___2. Control
___3. Equivocal
___4. Unknown

4.3 Tabulation of events employed as endpoint for each treatment:
___1. Presented
___2. Not presented

4.4 Timing of events:
___1. Complete
___2. Available to reader
___3. Neither

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Pulsed Echo Doppler Measures of Cardiac Stroke Volume in Man

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Abstract

Pulsed echo Doppler was evaluated in humans as a noninvasive technique to determine stroke volume. The flow velocity curves obtained from the ascending aorta by pulsed echo Doppler in six patients were correlated with simultaneously measured average stroke volume obtained by thermodilution. Atrial or ventricular pacing at multiple rates was performed in each patient and the average stroke volume varied from 49 to 111 cc in all patients and from 27% to 133% within each patient. In five of the patients, good to excellent correlations (0.65 to 0.94) were obtained. The sixth patient showed poor correlation. Therefore, pulsed echo Doppler can provide information to measure stroke volume in most individuals. The theory, possibilities and limitations in the use of this technique to noninvasively measure stroke volume are discussed.

Introduction

Since Doppler shifted ultrasonic waves reflected from moving red blood cells in the aorta provide information for the determination of the velocity of blood in that vessel, continuous wave Doppler techniques have been used as a noninvasive measure of cardiac output (1–5). However, as continuous wave techniques have fundamental limitations, we investigated the utility of range gated pulse echo Doppler in the determination of beat to beat stroke volume in man.

Materials and Methods

The commercially available ATL 500A Pulsed Echo Doppler used in our studies emits a 3.0 MHZ sound in pulses at a repetition rate of 10,000 per second (for the depth range of 5 cm used in our studies). By analyzing only sound returning after a specified delay from the initial emission, and knowing the velocity of sound in the medium, the device can be gated to analyze sound reflected from a specific depth, and therefore, within a specific structure. In practice, a 2 × 4 mm sample volume is obtained from which reflected sound is analyzed.

To evaluate the correlation of Doppler systolic velocity integrals with stroke volume, we compared them with simultaneously measured invasive average stroke volume in six patients at the time of cardiac catheterization (one patient) or immediately after mitral valve replacement (five patients). No patient had coronary artery disease, aortic or tricuspid valvular disease. Simultaneous invasive and noninvasive measurements were obtained at baseline and at different pacing rates. Three patients were paced at four different rates, and one each at five, six and seven different rates respectively. After obtaining informed consent, a temporary bipolar pacing catheter was positioned in the right atrium under fluoroscopic control in the catheterization patient, while epicardial atrial and ventricular pacing wires were placed as per routine at the time of surgery in the five other patients. A Swan-Ganz flow directed thermodilution catheter was passed to the main pulmonary artery in all patients (6). Postoperative patients were studied while intubated, heavily sedated and mechanically ventilated. In three postoperative patients with normal sinus rhythm, atrial pacing was performed. Two patients with atrial fibrillation had ventricular pacing. Cardiac out-

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put determinations were obtained in duplicate or triplicate with iced saline by thermodilution while the patients were in their intrinsic rhythms and at each pacing rate. The average stroke volume at every heart rate was obtained by dividing the cardiac output by the heart rate.

In all patients the ascending aorta was scanned with the transducer at the suprasternal notch (Fig. 1) and threshold and gain settings were set to obtain the best signal to noise ratio and then held constant throughout the study in any given subject (7). Doppler spectral and analog velocity curves (Fig. 2) were obtained simultaneously with the thermodilution cardiac output determinations. Analog output was fed into an Irex strip chart recorder for hard copy reproduction. Simultaneously phonocardiograms and electrocardiograms were obtained in all patients. End-systole was taken at the point at which the analog curve crossed the baseline (zero frequency shift) and coincided with the aortic closure sound (A_2). Zero velocity was determined in each study by removing the transducer from the chest and recording the resultant straight line. The areas subtended by the analog curves were calculated using a trapezoidal approximation with the aid of a SAC GRAF/PEN on-line with a PDP 1170 computer. For each heart rate, the area under the analog curve of at least 25 beats (usually 40 to 55) was determined and the average area for all beats at each heart rate was calculated.

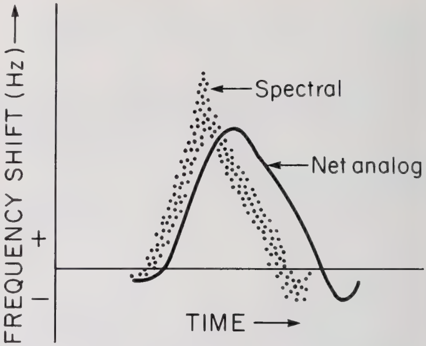

FIG. 2. Pulsed Echo Doppler's spectral and net analog output. Dots above the baseline represent movement towards the transducer (+ sign), while dots below the baseline represent movement away from it (− sign).

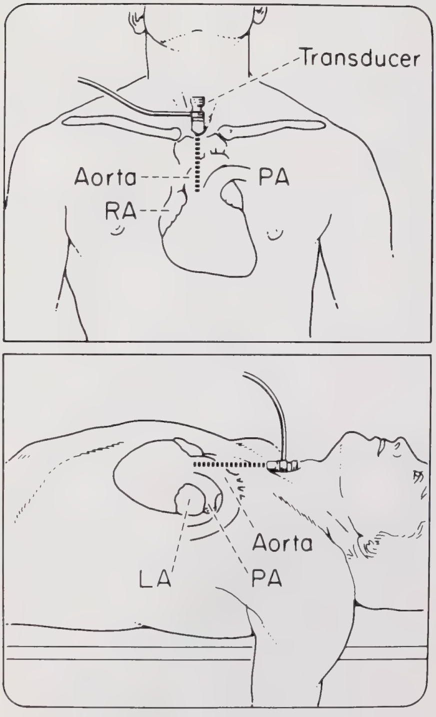

FIG. 1. Pulsed Echo Doppler transducer position for Scanning of the ascending aorta from the suprasternal notch.

Results

Adequate, reproducible Doppler curves were obtained from the ascending aorta in all patients. The lack of a zero baseline during diastole represents blood flow in diastole and echoes from moving tissue interfaces. These relatively small frequency shifts could be eliminated by lowering the threshold, reject, and line level settings. Flow curves showed distinct beat to beat variations in area that was cyclical with respiration, as found in previous studies using invasive flow determinations from the pulmonary artery and aorta (8, 9). Reverse flow was seen at end systole in the ascending aorta as would be expected (Fig. 3). As the beam was swept through the transverse aorta, simultaneous forward and reverse flow was seen; reverse flow was noted in the descending aorta.

With pacing, the average stroke volume varied from 49 to 111 cc in all patients, and from 27% to 133% within each patient (Table I). The average area under the Doppler curves for each heart rate was plotted against the measured average stroke

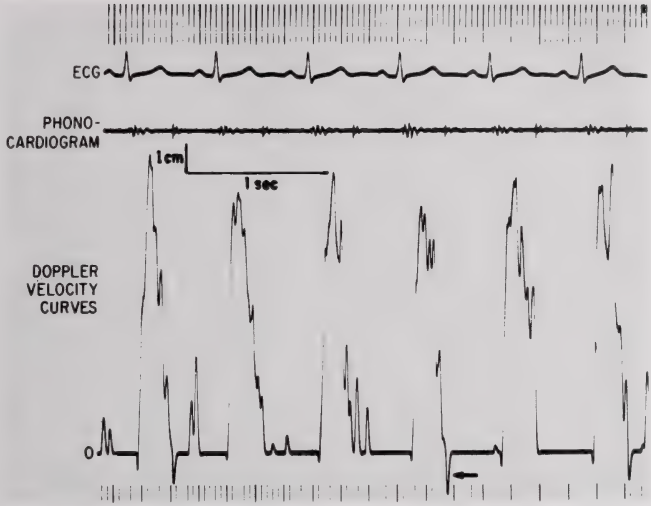

FIG. 3. Representative tracing showing the electrocardiogram, phonocardiogram and pulsed echo Doppler velocity curves from the ascending aorta. Reverse flow is seen at end-systole (arrow).

volume (Fig. 4) and least mean square linear regression analysis was performed. In five of the patients, linear regression analysis yielded good to excellent correlation (.65 to .94) between the average area under the Doppler curves and the average stroke volume at each heart rate (Table I). The remaining patient showed poor correlation. Analysis of the Doppler curves from this last patient revealed the expected wave form and typical respiratory variation expected in flow curves from the ascending aorta.

Discussion

We found that flow velocity curves obtained by pulsed Doppler techniques from the ascending aorta can be used as a measure of stroke volume in humans. The ability to obtain these curves from the ascending aorta in our patients avoided the need to approximate flow lost to the head and upper extremities when the transverse or descending aorta is sampled using the continuous wave Doppler (10). The analog output of the pulsed Doppler was thought to be a representation of the velocity profile of blood in the aorta. The blood flow per beat would be proportional to the product of the area under the analog flow velocity curve and the cross sectional aortic area in the region of interest, the latter remaining relatively constant (11).

Using invasive measures of stroke volume, five of six patients demonstrated good correlation between calculated stroke volume and Doppler velocity profiles. In the sixth patient, the flow velocity profiles were reproducible and of expected configuration. Audio evaluation indicated proper sound beam placement and physiologic variations were observed with respiratory cycles and potentiated beats. Therefore, the explanation for the lack of correlation in this case is unclear.

The use of continuous wave Doppler techniques as a measure of cardiac output is controversial (2, 3, 10, 12). Studying baboons, Huntsman et al (3) compared flows measured by an implanted aortic root electromagnetic flowmeter with continuous wave Doppler profiles obtained transcutaneously from the suprasternal notch. When they varied cardiac output with positive and negative drug interventions on ventricular performance, they found no proportionality between Doppler measure of stroke volume and those obtained invasively.

On the other hand, Sequeira et al (10) obtained flow velocity profiles transcutaneously from the descending aorta with a more advanced continuous Doppler system and compared these with

TABLE I

	Heart Rate beats per min	Thermodilution C.O. liters per min	Average Stroke Volume cc per beat	Average Doppler Area	R Value
Patient #1	90.0	8.06	89.6	0.945	0.15
	100.0	7.05	70.5	1.240	
	115.5	7.99	69.2	0.945	
	129.5	6.89	53.2	0.859	
	108.2	6.79	62.8	1.035	
	94.9	8.43	88.8	0.950	
Patient #2					
	68.0	5.13	75.3	0.688	0.94
	87.0	4.62	53.0	0.522	
	103.7	5.18	50.0	0.371	
	116.1	5.48	47.5	0.416	
	115.7	5.09	44.0	0.399	
Patient #3					
	88.9	4.13	46.5	1.120	0.75
	98.6	4.62	46.8	0.826	
	109.7	4.77	43.4	0.429	
	117.9	4.71	39.9	0.480	
	128.3	4.75	37.0	0.471	
Patient #4					
	54.1	6.02	111.4	0.723	0.66
	60.9	5.45	89.0	0.346	
	75.8	6.98	92.0	0.377	
	82.3	5.28	64.0	0.349	
	90.2	7.19	79.7	0.448	
	100.8	8.26	82.0	0.351	
	115.1	5.51	47.8	0.367	
Patient #5					
	82.7	4.55	55.0	0.606	0.66
	87.8	4.65	52.9	0.379	
	94.2	4.69	49.8	0.374	
	105.8	4.68	44.2	0.267	
	114.5	4.75	41.5	0.257	
	123.2	4.64	37.7	0.359	
	104.2	4.78	45.9	0.364	
	79.0	3.90	49.4	0.570	
Patient #6					
	105.0	5.80	55.2	.403	0.83
	112.6	5.60	49.7	.317	
	120.0	5.81	48.0	.353	
	130.0	5.92	45.0	.334	
	95.6	5.89	61.6	.403	

stroke volumes averaged from Idocyanine green cardiac output determinations in 20 patients. The aorta was measured from angiography at the presumed Doppler sampling site and an aortic cross sectional area calculated. The incident sound beam was assumed to be parallel to blood flow thereby allowing for quantification of flow volumes. Assuming that 25% of flow had been lost to the head and upper extremities, these authors found excellent correspondence between the Doppler and invasive methods. However, (0,0) points were assumed for the condition of no flow by both methods and greatly improved the correlation. Darsee et al (4) similarly found excellent correlation with cardiac outputs determined with continuous wave Doppler and Fick or thermodilution.

Pulsed echo systems hold theoretical advantages over continuous wave systems (13). Most importantly, continuous wave systems do not allow for assessing the depth from which the frequency shifted signals are returning. Therefore,

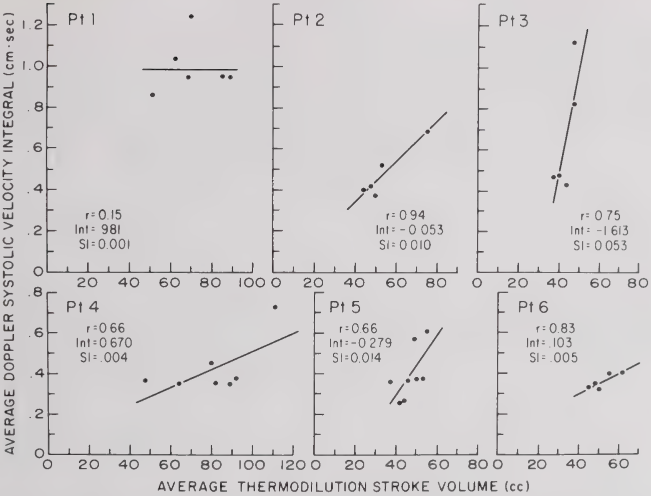

FIG. 4. Results obtained from each of the six patients comparing average thermodilution stroke volume to average Doppler systolic velocity integral. Regression lines are shown for each curve.

all structures moving within the ultasonic beam will return Doppler signals that may interfere with measurement of flow in the region of interest. In contrast, pulsed echo Doppler has a small sample volume that can be positioned along the beam path allowing for more selective sampling.

There are few published reports of attempts to quantitate flow in the great vessels with pulsed echo Doppler although this technique has been used in the qualitative assessment of valve lesions and intracardiac shunts (14–16). Angelson et al (17) using a pulsed echo system reported their experience in humans with flow velocity profiles from the aorta. Their approach too was from the suprasternal notch but acceptable profiles were obtained only from the transverse aorta. No comparisons with other measurements of aortic flow were made but this group demonstrated the ability of their system to measure flow in an in vitro model. Magnin et al used pulsed Doppler techniques combined with 2-D echocardiography to obtain velocity profiles from the ascending aorta just above the valve leaflets (18). They obtained excellent correlation, however, cardiac output determinations were not done simultaneously but rather within 24-hours.

Our study demonstrates the feasibility of obtaining reproducible pulsed Doppler flow patterns from the ascending aorta in vivo. The flow patterns correlate with changes in cardiac output and also seem to be sensitive to beat to beat changes in stroke volume; however, in these preliminary studies in humans we have not obtained as good correlation as in open chested dog experiments in our laboratory (19).

The difficulties in developing bedside usability of pulsed Doppler techniques includes accurate parallel alignment of the sound beam to aortic flow and positioning of the sample volume away from the aortic walls where wall motion artifacts and rapid fall off in blood velocity may introduce measurement errors. Moreover, cross sectional aortic diameter must be obtained and also, accurate spectral analysis of Doppler frequency shifts is necessary.

Sound beam alignment in our study was accomplished by listening for the highest frequency shift obtainable by scanning across the vessel and holding this position during the recording period. Concommitant use of 2-D echocardiography may allow more precise alignment as well as accurate measurement of aortic cross sectional diameter (20).

Ling et al (21) using invasive techniques in animals have shown that velocity in the proximal aorta is indeed uniform across the lumen, with rapid fall off only near the vessel wall. This observation may obviate the need to integrate flow velocities as a function of radius in the aorta. Finally, the incorporation of microprocesser technology to perform on-line instantaneous fast—Fourier spectral analysis of Doppler shifted frequencies may be the technological step necessary to permit accurate non-invasive determination of cardiac output in the clinical setting (22).

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Tuberculosis in East Central Harlem and Its Problems

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Abstract

Tuberculosis presents a major problem for the inner city population living in East and Central Harlem, in New York City. The characteristics of 135 patients are described. A majority of these individuals are chronic alcoholics, narcotic addicts, or both. As a result of noncompliance with antituberculous chemotherapy in these patients, the incidence of resistant tuberculosis is emerging as a real threat.

Introduction

Tuberculosis is still the most prevalent chronic communicable diseases in the inner city areas of the United States. In 1973, nearly one-half of the new tuberculosis cases occurred in cities with populations of 100,000 or more (1).

Joint Diseases North General Hospital, located in East Harlem, serves one of the most economically depressed section of the city. A very high fraction of the patients are alcoholics and/or drug addicts.

Alcoholism constitutes a special problem in the treatment of tuberculosis. Among alcoholics the incidence of tuberculosis is inordinately high. In keeping with the addiction and life style of alcoholics, their treatment is often irregular, incomplete and haphazard. As a consequence, their organisms become resistant to therapy.

We surveyed the records of all patients with tuberculous admitted between 1974 and 1979.

Materials and Methods

In this six-year survey, only those patients with positive cultures or histology were included. Their records were studied for age, sex, alcohol, and/or drug addiction, and site of the diseases. Roentgenograms were reviewed to determine the latter. The outpatient clinic charts were reviewed for their follow-up in the pulmonary and other clinics. Whenever a patient failed to keep an appointment to the clinic, a letter or telegram was sent to his or her address, and the Board of Health was notified. Follow-up was considered to be incomplete only if the patient failed to return to the clinic for more than three months.

Sociodemographic Characteristics of the Patients

One hundred thirty-five patients were included in this study. Thirteen patients (9.6%) were below the age of twenty-four, sixty-eight (50%) were between ages 25 and 49, and the remainder were 50 years of age and above. They included 84 men and 51 women. Most of the patients were Black (120); White and Hispanic people constituted the remainder. Fifty-five of our patients were alcoholics, twenty-four were alcoholic and drug addicts, and two were drug addicts, but not alcoholics. Thus, 81—60%—of the patients were alcoholics and/or drug users (Table I).

Distribution of Tuberculosis

The lungs were the most common site (110). The apico-posterior segment was the most frequently involved region in the lung (78). However, involvement of other areas was not uncommon. Thirteen patients had diffuse alveolar infiltrates, six had miliary tuberculosis, twelve had lower lobe involvement, and six had involvement of the anterior segment of the upper lobe. Contrary to accepted belief, the middle lobe was involved in only one patient (Table II).

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TABLE I
Sociodemographic Characteristics of Tuberculous Patients

	Age				Sex		Race			Addiction		
Year	No.	0–24	25–49	50 & above	M	F	B	W	O	Alcoholic & Drug	Alcoholic	Drugs
1974	19	0	8	11	12	7	14	2	3	2	5	—
1975	23	2	15	6	15	8	20	2	1	6	5	—
1976	22	4	11	7	12	10	20	0	2	4	10	—
1977	29	2	12	15	17	12	28	1	0	6	13	—
1978	20	4	10	6	12	8	17	2	1	3	10	1
1979	22	1	12	9	16	6	21	1	0	3	12	1

TABLE II
Pulmonary Tuberculosis: Distribution According to Site

				Upper Lobe			
Year	No.	Miliary	Diffuse	Ant.	Apico-Post	Middle Lobe	Lower Lobe
1974	11	—	—	—	11	—	—
1975	17	1	3	1	10	—	2
1976	18	1	3	—	11	—	3
1977	27	2	4	3	14	—	4
1978	18	0	1	0	17	—	1
1979	20	2	2	2	15	1	2

Extrapulmonary tuberculosis was also frequently seen. Nineteen patients had skeletal tuberculosis; lymph nodes were involved in seven, the pleura in six patients, CNS and peritoneal involvement each was seen in two patients, and pericardial and renal involvement each was seen in one patient (Table III).

Nine of our patients died. Two deaths were unrelated to tuberculosis. In six, tuberculosis was considered to be the primary cause of death and, in one, it might have contributed to death.

Follow-up study of 126 surviving patients showed that 65 (49%) failed to complete chemotherapy and, of these, 26 were alcoholics, 17 were alcoholics and drug addicts, and two were drug abusers. This constituted 72% of the noncompliant group. In the compliance group, 48% were alcoholics and drug addicts.

Data on Sensitivity Study

Data on susceptibility of tuberculosis strains to antitubercular drugs from 1974 through 1979 showed a trend toward resistance to Rifampin (RIF) and Ethionamide (ETH) during 1978 and 1979. All Rifampin resistant strains appeared during 1979 and represented 28% of the fourteen strains tested that year. Most resistance developed toward Ethionamide and was demonstrated by six of the fifty-two strains (12%) treated during the six-year period (Table IV).

Discussion

Tuberculosis appears to have retreated into pockets of densely populated areas. The residents of which confront poverty, unemployment, overcrowding, alcoholism and protein-calorie malnutrition (2–5). In the inner city, tuberculosis is then a disease of homeless and displaced persons (6). Immigrants are a continuing source of infection (7).

Our study showed that among the group we treated for tuberculosis, 60% were chronic alcoholics and narcotic addicts.

Noncompliance, in terms of both regularity as well as completion of chemotherapy among our patient population was inordinately frequent.

TABLE III
Distribution of Tuberculosis

Year	Total No. Patients	Lung	Pleura	Bones	Lymph Nodes	CNS	Other
1974	19	11	1	7	—	—	1 (Renal)
1975	23	17	—	2	2	1	—
1976	22	17	—	3	1	—	1 (Peritoneum)
1977	29	27	2	3	—	—	—
1978	20	18	2	3	3	—	—
1979	22	20	2	1	1	1	2 (1-Pericardial) (1-Peritoneum)

TABLE IV

Data on Sensitivity Study

Year	Strains Tested	Strains Resistant					
		INH	SM	PAS	ETH	EMB	RIF
1974	2	0	0	1	0	0	0
1975	10	0	0	0	0	0	0
1976	7	0	1	0	0	0	0
1977	5	1	1	0	1	0	0
1978	14	1	0	0	2	0	0
1979	14	1	1	1	3	0	4
Total Number	52	3	3	2	6	0	4

Forty-nine percent of all patients failed to complete chemotherapy, and of these, 72% were chronic alcoholics and narcotic addicts.

As a result of noncompliance, the incidence of resistant tuberculosis has emerged as a significant threat.

These patients go from hospital to hospital, often failing to complete the necessary studies, thereby delaying diagnosis and treatment until the tuberculosis is far advanced. Many of these patients, even after treatment is started, sign out against medical advice.

Inaccurate information given by the patients such as denial of previous hospitalization for tuberculosis, incorrect statement as to date of birth, name and address add to the difficulties in producing loss of time due to repetition of test. Longer hospital stays and time is lost in pursuit of these patients or their contacts. Many of these patients have no permanent residence and require help to obtain care.

An organized, easily accessible source for receiving their medication and monitoring their compliance is needed. Fortunately, the pulmonary Division has recently established an epidemiologic "Hot Line" in the private and voluntary sector for field follow-up of delinquent patients. Any diseased suspect case that is delinquent and has not completed nine months of INH/RIF (with a minimum of six months), since the last positive smear, pending cultures or culture positive is a candidate for field follow-up by the Division.

A Supervised Therapy Program (STP) has been established by the Division to:

1. Locate potential candidates.
2. Establish a specific time and place for delivery of medications to STP patients, and witness the patient's ingestion of medications.
3. Document thoroughly on a daily basis all services provided such as drugs, sputum, etc.
4. Establish liason with public and private community facilities who have a relationship to the patient.
5. Inform STP office immediately when a potential candidate has been located and accepted in STP.
6. Carry out contact follow-up.

We hope, the follow-up care of the tuberculous patients will be improved in the future.

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Computerized Tomography of the Spine in Metastatic Disease

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Abstract

Twenty patients with metastatic malignancy of the spine were evaluated by CT and the results were compared with conventional radiography. In 12 cases, the plain radiographs were either negative or the abnormalities could not explain the clinical symptoms. In five cases, spinal canal compression was proved by the presence of intruding material formed of tumor or bony fragments. In all instances CT outlined in further detail the destruction of the vertebral body and the posterior elements. It also demonstrated the paravertebral extension of the tumor if that was present. CT is a superior noninvasive procedure in the evaluation of metastatic lesions of the spine and spinal canal. It may replace tomography and, in many instances myelography, a potentially dangerous procedure, can be avoided.

The introduction of Computerized Tomography (CT) has expanded our understanding of various anatomic structures and now, virtually every system of the body has been subject to this new technique.

Because of its inherent anatomic structures, the abnormalities of the vertebral column and pelvis are only partially visualized by conventional radiography, therefore scanning the spine by CT technique has rapidly gained in popularity. CT is a noninvasive procedure that defines abnormalities–localized by conventional radiography–in further detail. It may demonstrate narrowing and expansion of the spinal canal, of the sacral and intervertebral foramina and effectively displays both the bony and soft tissue components in trauma, inflammatory and metastatic lesions.

The purpose of this paper is to describe our experience with CT of the spine in the evaluation of metastatic extension to and around the spinal bony structure. Representative cases will be described in detail.

Materials and Method

Between December 1979 and October 1980, 20 patients with metastatic malignancy to the spine were evaluated by computed tomography at The Mount Sinai Hospital in New York. The CT was performed either by the Ohio Nuclear Delta 50 Body Scanner or by the Pfizer 200FS. The patients were examined supine and 8mm consecutive scans were taken over the involved area. Usually five to seven vertebral levels were covered. The scanning times on the Ohio Delta 50 were three minutes and on the Pfizer, 32 seconds. In each patient, CT was preceded by conventional radiographs (AP and lateral views) for determining the level of the lesion and minimize time and expenses. In some of the cases, tomograms of the involved area and myelography were performed.

The patients' ages ranged between 50 and 84 (Table I). Eleven patients were female, nine were male. Four patients had known primary breast cancer. Two had carcinoma of the lung, two had suffered from hypernephroma, and each of the remaining six patients had either leukemia, cancer of the pancreas, of the uterus, ovary, colon, or the prostate, respectively. Three patients had multiple myeloma and in three instances the primary tumor had been unknown at the time of the examination.

Case Reports

Case 18 (Chosen as representative)

A 68-year-old male presented with back pain radiating to the right flank and right buttock. He was previously treated by his private physician

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TABLE I

Clinical and Radiologic Data in 20 Patients Evaluated for Metastasis to the Spine

No./Age/Sex	Symptoms/Signs	X-ray	CT	Diagnosis
1/84/F	Left foot pain	Indistinct trabeculation L5-S1	Extensive destruction of L5 and sacrum	Ca breast
2/56/F	Low back pain	L3 left pedicle indistinct	Sagittal fracture of body of L3.	Ca breast
3/56/F	Cauda equina syndrome	Negative. Myelography; compression of pantopaque column	Destruction of posterior aspect of L4-5.	Ca breast
4/68/F	Low back pain	Compression of L2 sclerosis	Spinal canal O.K.	Ca breast
5/50/M	Back pain and leg weakness	Lytic lesion of D6.	Epidural fat obscured on left	Ca lung
6/74/F	Absent	Small defect of left inferior process of L2.	Extraosseous soft tissue mass	Ca lung
7/58/F	Back pain and leg weakness	Lytic lesion left side of L1	Extensive destruction of L1 with soft tissue mass. Not infiltrating.	Hypernephroma
8/56/F	Neck and arm pain	Lytic lesion of C7	Extensive destruction C7, T1, T2. Compression of spinal canal	Hypernephroma
9/63/F	Back pain & both leg weakness	D5, 8 & 11 compression myelography: Negative	D8 epidural space obliteration	Ca pancreas
10/80/F	Limb pain	No destruction	S1 & 2 destruction left	Ca colon
11/74/M	Limb pain	Lytic lesion of D6, 7 & 8	Destruction of posterior aspect of the body of D8	Ca prostate
12/74/F	Back pain and leg weakness	Lytic lesion of L2 & 3	Very extensive destruction, saggital fracture of body of L2	Ca uterus
13/64/F	Leg pain	Osteolytic lesion of right side of L3	L3 destruction large soft tissue mass extends into canal	Ca ovary
14/57/M	Back & hip pain, both leg weakness	Compression of T11	Bony fragments extend in the canal	Leukemia
15/55/M	Neck and arm pain	D1 lytic lesion	C7, D1 destructive mass extends into the spinal canal	Multiple myeloma
16/76/M	Back pain, both leg weakness	Lytic changes of the body of L5	Extensive destruction. Spinal canal is open. Erosion of sacrum	Multiple myeloma
17/59/M	Back pain	Lytic lesion of D9	Extensive destruction & compression	Multiple myeloma
18/68/M	Back pain	Lytic lesion on right side of the body of L1. Myelogram negative	Extensive dstruction, open canal	Unknown
19/67/F	Back pain	Lytic lesion of body of L1	Extensive destruction of L1 & 2. Extraosseal soft tissue mass	Unknown
20/50/M	Absent	D6 lytic	Destruction of posterior part of D6 with spinal canal involvement	Unknown

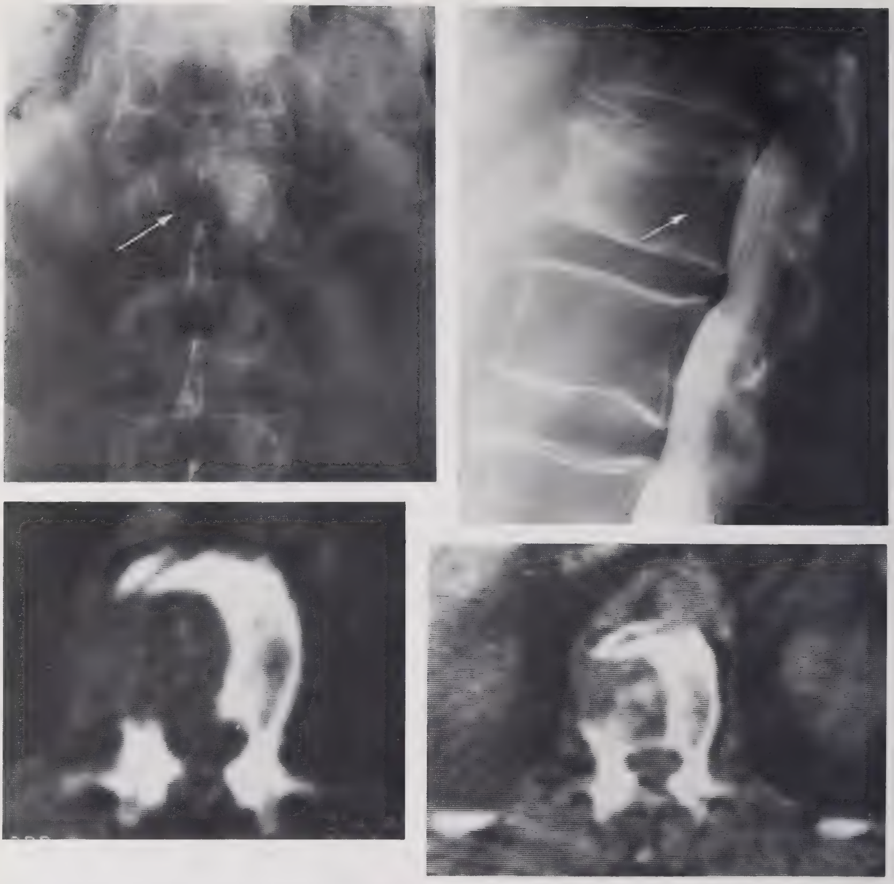

FIG. 1. (Case 18). Metastatic adenocarcinoma. A. Frontal view of the upper lumbar spine reveals a compression of the right side of the body of L1 (arrow). B. Lateral view; The posterior part of the body of L1 shows a lytic lesion (arrow). Metastasis. Note: No defect of the metrizamide column. C. CT at the same level; The right half of the body of L1 is destroyed. The spinal canal is opened. D. Six months after radiotherapy: L1 shows reossification.

for "arthritis." Physical examination revealed tenderness of the back and decreased sensation to pin prick in both feet.

Plain films of the lumbosacral spine revealed a defect of the right side of the body of L_1 (Fig. 1A). Myelography was performed and apart from mild anterior defects at the level of L_{4-5} it failed to reveal any abnormality at the above mentioned area (Fig. 1B). CT, however, showed an extensive destruction of L_1 with an open spinal canal (Fig. 1C). At biopsy metastatic adenocarcinoma was found without evidence of any primary lesion. The patient was treated with local radiotherapy. After several months the repeat CT showed reossification (Fig. 1D). The site of the primary tumor has remained unknown.

Case 10

An 80-year-old woman presented with pain radiating to the left gluteal area. Physical examination revealed weakness of the left leg. Sixteen months earlier the patient had undergone hemicolectomy for carcinoma of the descending colon. Plain radiograph of the lumbosacral spine failed to reveal any abnormality (Fig. 2A). CT demonstrated a diffuse increased radiodensity of

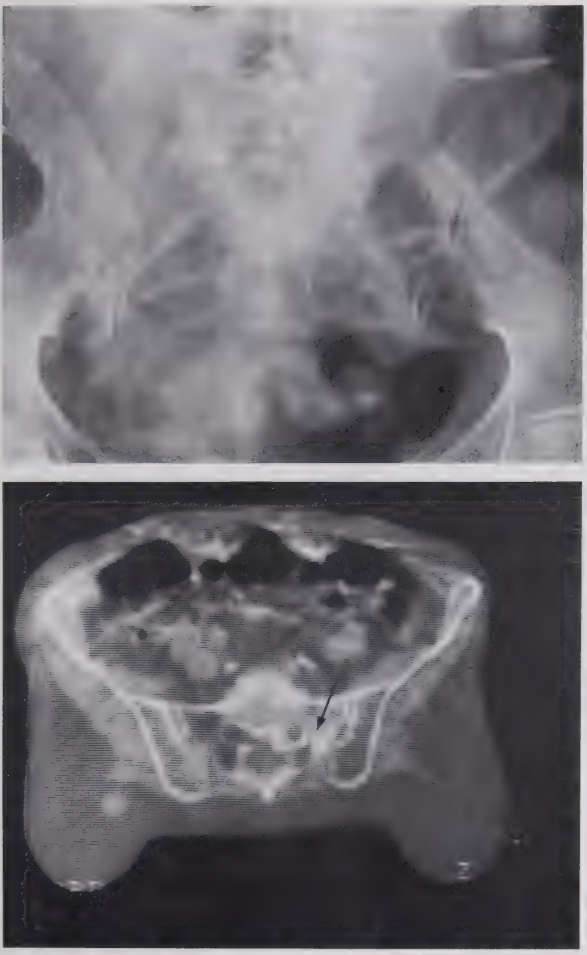

FIG. 2. (Case 10). Metastatic Colon Carcinoma A. Anteroposterior view of the sacrum fails to reveal abnormality. B. CT scan of the sacrum demonstrates an increased density involving the upper segment on the left (arrow). Osteoblastic metastasis.

the upper segments of the sacrum on the left side (Fig. 2B) suggesting metastasis.

Case 14

A 57-year-old male was admitted because of headaches, back and hip pain and weakness of both lower extremities. He had been diagnosed and treated for chronic lymphatic leukemia two years previously. Plain radiographs showed compression of the body of D_{11} with a slightly indistinct pedicle on the right side (Fig. 3A). CT revealed extensive destruction of the body of D_{11} with protrusion of some bony fragment into the spinal canal (Fig. 3B).

Results

Eighteen patients had complaints referrable to cord or root lesions such as back pain, neck and arm pain, leg weakness, or leg pain and bladder dysfunction (Table II).

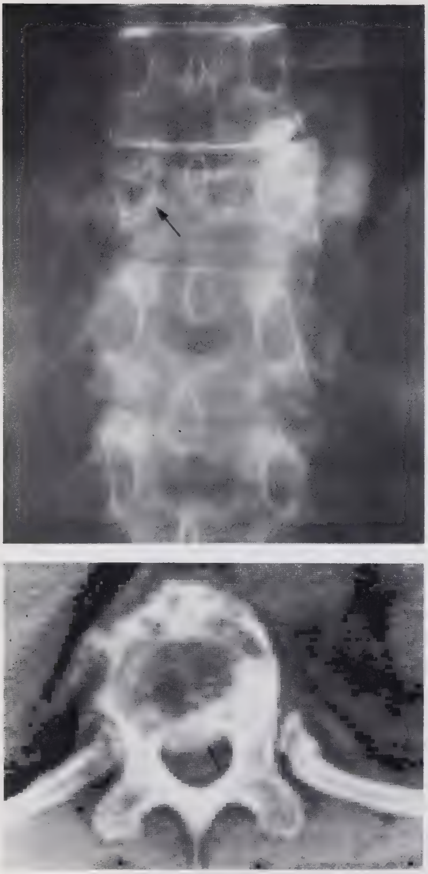

FIG. 3. (Case 14) Lymphatic Leukemia A. Anteroposterior view of T11 reveals compression. The right pedicle is indistinct (arrow). B. CT scan of T11 shows in addition to the destruction of the vertebral body protrusion of a bony fragment into the spinal canal (arrow).

Back pain with weakness of both legs was the most common presentation (6) followed by back pain alone (5), limb pain alone (4), and neck pain or limb pain respectively, without weakness (2). Two patients had no neurologic complaints or findings and one patient with cauda equina syndrome presented with loss of control of bowel and bladder function of two years duration. All patients were ambulatory or could stand during the neurologic examination. In only two cases were symptoms referrable to pathology present in the cervical spine.

TABLE II
Metastasis to the Spine

Clinical Signs and Symptoms:	No. of Cases
Back pain and both leg weakness	6
Back pain alone	5
Limb pain alone	4
Neck, arm pain	2
Cauda Equina Syndrome	1
No neurologic symptoms	2

In 12 cases, the plain radiographs were either negative or the abnormalities could not explain the clinical symptoms. In two cases CT demonstrated a sagittal fracture of the body which extended into the spinal canal at the level of L2 and L3 respectively. In five patients, the spinal canal was compressed, as demonstrated on CT by the presence of intruding material formed of tumor or bony fragments (Table I). In all cases, CT outlined in further detail the destruction of various parts of the spine.

The size of the spinal cord proper could not be directly appreciated on the CT images with the present equipment.

Discussion

The advantage of computerized tomography of the spine has been discussed by various authors in cases of trauma, primary neoplasm and inflammatory diseases (1–4).

CT defines in further detail abnormalities localized by conventional radiography. It allows evaluation of the craniocaudal extent of the lesion as well as the relationship of the lesion to the surrounding spinal soft tissue and the spinal canal.

Lee (5) found that CT is helpful in localizing fatty tissue within the subarachnoid and epidural spaces using its low attenuation values. Our experience correlated well with the findings of Roub et al (6) whereby CT better demonstrated the pathologic anatomy than did conventional radiography, including tomography.

Utilizing both narrow and wide window techniques, small bony fragments were recognized and differentiated from the soft tissue mass (Fig. 3B). When the tumor involved the posterior aspect of the vertebral body or the posterior elements, CT demonstrated clearly the intra and paravertebral extent of the lesion (Fig. 4, Case 13) (7). CT was particularly helpful in outlining three dimensionally the spinal canal, which can-

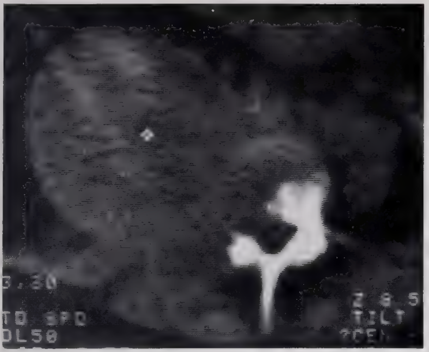

FIG. 4. (Case 13) Metastatic carcinoma of the ovary. CT scan at the level of L3 shows a large soft tissue mass on the right side with destruction of the vertebra.

not be well seen with any of the available conventional techniques. Thin layers of paravertebral mass indicative of the extent of pathology can be visualized only by CT (See Table II and Figures 1C and 3B).

All of our patients had metastatic carcinoma to the spine and most of them had been so suspected by x-ray findings.

The ideal sequence of work up in such patients with known primary and suspicious bone lesion with or without symptoms would include an AP and lateral x-ray of the spine followed by CT. This sequence may provide a rapid diagnosis and allow for therapeutic strategies within a few hours. Painful and potentially dangerous procedures such as myelography could be eliminated.

In our opinion CT is a superior, noninvasive procedure in the evaluation of destructive lesions of the spine and spinal canal. It may display bony and soft tissue components of tumorous lesions. It can be performed safely and quickly in patients with metastatic disease and provide adequate information for treatment planning as well as a follow up of response to therapy (Fig. 1D) (6). In most cases, it may replace tomography and in many instances myelography can be avoided.

We feel that myelography is indicated only if the lesion is visualized by conventional technique but the CT does not explain the neurologic symptoms, if multiple cord levels are present or if an extensive cord lesion is suspected. In the presence of an incomplete block, myelogram may delineate the extent of pathology.

If, in spite of radiotherapy, the patient deteriorates and the neurologic findings worsen, a myelography with spinal fluid examination should be performed.

The indication of laminectomy is beyond the scope of this communication but we believe that neurosurgical consultation should be obtained once neurologic dysfunction is present in patients similar to ours.

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Spontaneous Perforation of Intestinal Duplications

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Abstract

Intestinal duplications are uncommon malformations, usually seen in children. While the pathogenesis of these lesions is unknown, many are found to contain heterotopic, most commonly gastric, mucosa. A case of a perforated ileal duplication in a 67-year-old man is described. There was no evidence of gastric mucosa or peptic ulceration in the lesion. This is one of the oldest patients ever to develop acute symptoms from an intestinal duplication, and one of the few to perforate in the absence of peptic ulceration. Current theories regarding embryogenesis, malignant potential, and surgical management are discussed.

Duplications of the alimentary tract are uncommon and usually present in early life; of 78 duplications in children, 60 percent were diagnosed before six months, and 85 percent before two years of age (1). Despite many theories, the pathogenesis of these anomalies has not been satisfactorily defined (2–6). The lesions can be either tubular or spherical and can arise from any portion of the gastrointestinal tract (7), with a strong predilection for the ileum in children (1, 7, 8). In adults, duplications are seen mostly in the posterior mediastinum (9), because in this location they may remain asymptomatic beyond infancy and childhood.

Duplications are usually fused with the adjacent intestine, but in some cases the attachment can be very narrow, and occasionally they can be completely separate. They are composed of a muscular wall lined with intestinal, or rarely, respiratory epithelium. Communication with the adjacent intestine can be demonstrated in approximately 20 percent of cases (10).

In a collective review of 63 adult intestinal duplications, only 14 patients were older than 50(9). Ten of these 14 patients had duplications of the esophagus, stomach or duodenum and only three of the ileum; two of the ileal duplications presented as an abdominal mass and bowel obstruction, respectively, and one was found at autopsy. In general, mid- and hindgut duplications present most frequently as an abdominal mass or intestinal obstruction (8). About 50 percent of ileal duplications contain ectopic gastric mucosa (11) and may manifest peptic ulceration (12) or intestinal hemorrhage (13), in addition to the described features.

A case of a 67-year-old man with peritonitis due to a perforated duplication of the ileum is presented. There was no evidence of communication with the adjacent intestine and no gastric mucosa could be identified within the duplication.

Case Report

A 67-year-old Caucasian male was admitted because of a four-day history of abdominal pain. On the day of admission, he had vomited, developed diarrhea, and reported having chills and feeling feverish. Eighteen years before, he had consulted a physician because of abdominal pain. At that time, he underwent upper and lower gastrointestinal x-ray contrast studies and was told that he had a "spastic colon." The pain resolved without treatment and he has remained healthy until now.

At the time of this presentation, his rectal temperature was 40° C and his pulse rate 120 per minute. Examination revealed direct and rebound tenderness, especially in the right lower abdomen. A fullness was appreciated, but no definite mass was felt. Bowel sounds were absent.

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Rectal examination was normal. The hemoglobin was 15.5 g. The total white cell count was 15,300 with 50% polymorphonuclear leukocytes, 39% band forms, 4% lymphocytes, and 7% monocytes. Serum electrolytes and urinalysis were normal. The electrocardiogram showed sinus tachycardia without evidence of ischemia. Chest x-rays and scout films of the abdomen were unremarkable.

The patient was thought to have ruptured appendicitis and an emergency operation was performed. A McBurney incision that revealed purulent peritonitis without appendicitis was closed and laparotomy through a right paramedian incision revealed diffuse purulent peritonitis. There was a mass near the mesenteric border of the ileum about 40 cm proximal to the ileocecal junction, with free perforation at that site. The remainder of the small intestine and colon was normal. The gallbladder was tense but not inflamed from a solitary large stone impacted in its neck. A segment of ileum, approximately 20 cm on each side of the mass was resected, and an end-to-end, two layer anastomosis was constructed. The gallbladder was aspirated and found to contain white bile. A cholecystostomy tube was inserted through the fundus after extraction of the obstructing stone. The patient recovered uneventfully.

Pathologic Findings

The gross specimen consisted of a soft, submucosal cyst-like cavity filled with creamy, white purulent material, measuring 2.5 cm in diameter (Fig. 1). The cavity was located along the mesenteric border of the adjacent ileum. Because of its distension it caused stretching of the overlying small bowel mucosa. There was no communication between the normal ileum and the cyst; however, a sinus tract was seen coursing from the cyst through the periserosal fat, which was indurated and focally covered by fibrinous material.

Microscopically, the lesion was typical of a duplication cyst lined with ileal mucosa identical to the mucosa of the adjacent intestine. No gastric mucosa was seen. There was evidence of acute inflammation extending from the mucosal surface to the muscularis propria. Linear streaks of inflammatory cells, consisting largely of eosinophils and mononuclear cells extended through the muscularis propria. The outer layer of the muscularis propria was seen to divide as it approached the duplication, joining with another muscular coat of the lesion (Fig. 2). The cyst was surrounded by smooth muscle except in a single area where there was no muscular coat. There was a sinus tract extending into the serosal fat, which was acutely inflamed. There was evidence of acute serositis.

Discussion

The term duplication was first used by Fitz (14) to describe cystic lesions that he misinterpreted as remnants of the omphalomesenteric duct. Until the 1950's, terms such as enterogenous cysts, giant diverticula, ileum duplex, thoracic cysts of enteric origin, unusual Meckel's diver-

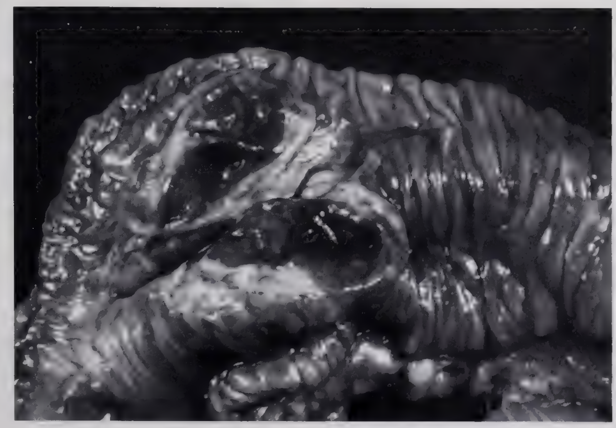

FIG. 1. Photograph of the gross specimen showing mucosal surface of normal ileum and the duplication cyst opened to reveal a cavity which has been evacuated.

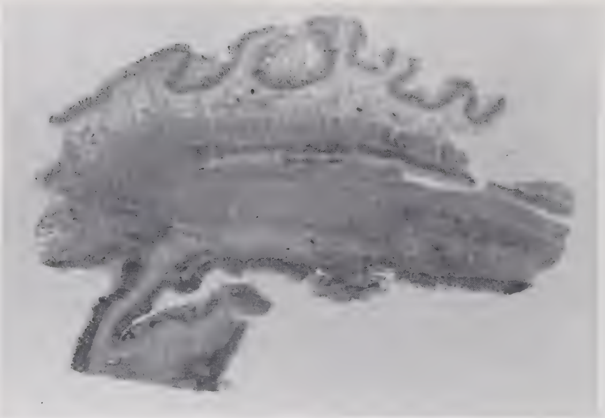

FIG. 2. Whole mount of the specimen with normal ileal mucosa at the top and mucosal lining of the cyst at the bottom. The muscularis is seen to divide so that the cyst as well as the adjacent intestine each have separate muscular layers (hematoxylin and eosin).

ticula, and gastric thoracic cysts were used to describe different manifestations of this entity. In 1937, Ladd proposed that these should be grouped as duplications for simplicity and clarity, because he believed they have a common morphology and embryonic derivation (15). As a result of the work of Ladd and Gross (16, 17), the current terminology has been adopted; however, it is doubtful that all of these anomalies have a common pathogenesis.

Edwards believed that duplications result from abortive twin formation that occurred so late in development that the effect was confined to a limited intestinal segment (3). Ravitch also believed that colonic duplications associated with doubling of the genito-urinary tracts and spine, were the result of partial twinning or incomplete fusion of two individuals (18).

Lewis and Thyng (2) noted frequent outpouchings in the fetal alimentary tracts of pigs, rabbits, and humans. They proposed that a duplication could result from sequestration of such protrusions. However, this theory lost favor when it was realized that these evaginations were almost always on the antimesenteric side of the bowel (as is Meckel's diverticulum), while duplications are usually found along the mesenteric border (7).

In 1944 Bremer (4) proposed that intestinal duplications result from failure of normal vacuolization. He noted that, during the sixth week of embryonic life, there is a rapid proliferation of intestinal epithelial cells which may occlude the intestinal lumen. Normally the lumen is reestablished by the formation and coalescence of vacuoles. He theorized that abnormalities in this process could lead to chains of fused vacuoles separate from the main lumen, and thus result in the formation of intestinal duplications. There is, however, little evidence that luminal occlusion or significant vacuolization occurs in intestinal segments other than the duodenum (19).

Vaage and Knutrud contended that several mechanisms can be invoked to explain the pathogenesis of intestinal duplications (6). The split notochord syndrome resulting from a primary splitting of the notochord and the persistence of a partial or complete enterocutaneous fistula would best explain the situations in which intestinal duplications coexist with urogenital (18) or vertebral (20) anomalies. A tracheo-broncho-foregut duplication, which results from partial regression of what otherwise would be a tracheo-esophageal fistula, would best explain those foregut anomalies not associated with vertebral defects. Furthermore, the authors accept Bremer's theory of disordered vacuolization as valid in certain instances of intestinal duplication.

Favara argued that some intestinal duplications could be explained on the basis of a vascular etiology (5). In a review of 37 pediatric intestinal duplications, he found associated intestinal atresia in four, ileal stenosis in one, and short small bowel in two. The association of duplications with these lesions, all of which may result from intrauterine ischemia, may indicate that enteric duplication could be another consequence of prenatal bowel infarction.

While a number of these theories are appealing, at present, the pathogenesis of intestinal duplication has not been conclusively established (11).

There are a number of other important features of intestinal duplications. As many as 50 percent of these structures may contain ectopic mucosa, which is usually gastric in morphology and function; duplications containing mucosa of respiratory, pancreatic, colonic, gallbladder origin, and ectopic adrenal cortex have also been reported (1, 7–9). The presence of gastric mucosa may lead to peptic ulceration and bleeding, especially in the distal small bowel where the mucosa is particularly vulnerable to acid-pepsin secretions. As a result, tubular duplications are more likely to present with occult gastrointestinal bleeding because they communicate with the adjacent intestine more often than the spherical (11). However, cases presenting with massive melena have been described (13). The spherical noncommunicating duplications by virtue of their size and/or location, more commonly present as a painful mass or intestinal obstruction.

In 1975, Orr and Edwards summarized eight cases of carcinoma arising in intestinal duplications, all of which contained either gastric, colonic, or esophageal mucosa (21). Whether or not the sequestered mucosa inside a duplication has a propensity to malignant degeneration is unknown. It is not in contact with the intraluminal potential carcinogens, such as bile acids (22); however, other mechanisms may play a role. Since such a small percentage of intestinal duplications are seen in adults, the propensity for duplicated mucosa to undergo carcinomatous transformation may actually be substantial.

The diagnosis of intestinal duplication is rarely made preoperatively. When there is communication with the normal lumen, barium can occasionally be seen within the duplication (23, 24). Duplications containing gastric mucosa may be diagnosed by pertechnetate ^{99m}TC scanning (11, 25), however the distinction from Meckel's diverticulum is virtually impossible.

Intraoperative decisions must be made with special regard for the pathologic anatomy of intestinal duplications. The most important consideration is that duplications, especially those fused with the adjacent intestine, share a common wall with that intestine and dissection in this plane is likely to result in penetration into the lumen (16). Secondly, the proximity of the duplication to the mesentery and the common blood supply with the adjacent bowel may lead to ischemia, if attempts are made to resect the duplication alone (26).

For duplications located in the jejunum, ileum or colon, resection and end-to-end restoration of bowel continuity is the procedure of choice, when feasible (8). Duplications not closely adherent to adjacent bowel may be resected without removal of normal intestine (27). Gastric duplications are best managed by excision of the lesion together with adjacent normal stomach wall and closure of the resulting defect (26, 28).

Intrathoracic duplications of the esophagus are often the most difficult and technically demanding. In tubular duplications, accidental entry into the esophageal lumen may result in mediastinitis. If the lesions are to be excised, meticulous dissection must be carried out. In some cases it is sufficient to excise only the mucosa of the duplication together with the remainder of the lesion (1). In adults many of these duplications do not communicate with the esophagus and their cystic nature lends itself to excision without great difficulty (9).

In other locations, cystenterostomy (29), distal fenestration (1), and excision of the common wall (17), have been successfully applied. It has been suggested that duplications of the colon may be premalignant (21), a concept that may influence the extent of resection (1).

The case presented here is noteworthy in several respects.

He is the oldest patient reported with acute symptoms from an intestinal duplication in whom the diagnosis was made antemortem. While there have been several reports of patients over the age of 50, almost all had symptoms related to an abdominal mass or intestinal obstruction. An example is a patient reported by Nolan and Lee in whom a cystic duplication of the ileum was the lead point of an ileo-ileal intussusception resulting in intestinal infarction. In that case, the preoperative diagnosis was also thought to be acute appendicitis (26).

In fact, it is exceedingly rare for intestinal duplications to spontaneously perforate and cause peritonitis, especially in the adult. While others have indicated that such a presentation is possible, there are few reports of such cases, in the absence of peptic ulceration. In 1952, Gross described a perforated jejuno-ileal duplication in a one-month-old infant that contained only small intestinal mucosa (7). As of 1966, he had compiled 140 duplications in children (23). Only two of these had perforated, and both were secondary to peptic ulcers. In Bower's review of 78 duplications in a pediatric population, he does not describe a single case of peritonitis (1). Similarly, no case of peritonitis from perforation was found in Anderson's review of 63 cases of intestinal duplication in adults (9). In 1966, Houston (30) found only six reported cases of perforated intestinal duplication. Gordimer and Bluestone (31) reported a perforated duodenal duplication that contained gallstones and only duodenal mucosa. Schein and Grundfest (32) described a perforated ileal duplication in which, as the result of severe inflammation, no mucosa was identifiable. Edwards (3), Stagg and Lynn (33), Gohn (34), and Collins (12) have all described duplications containing gastric mucosa which perforated as the result of peptic ulceration.

In this case the duplication contained only normal ileal mucosa and we do not know why it spontaneously perforated. The patient's symptoms eighteen years prior to admission may have been related to the duplication. Transient incomplete obstruction or intussusception could have produced abdominal pain at that time.

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Oral and Ambulatory Therapy of Listeria Bacteremia and Meningitis with Trimethoprim-Sulfamethoxazole

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Abstract

Two patients, one with meningitis and the other with bacteremia due to *Listeria monocytogenes,* were treated successfully with the combination of oral trimethoprim and sulfamethoxazole. Cultures had been positive in both patients despite previous therapy with other antimicrobial agents. The patients were fully ambulatory during the course of treatment with oral trimethoprim-sulfamethoxazole. This drug combination may be useful in patients with Listeriosis that fails to respond to other antimicrobial agents.

Listeria monocytogenes is a small, gram-positive coccobacillus whose spectrum of infection in man includes perinatal infections, meningitis, conjunctivitis, endocarditis and osteomyelitis (1, 2). The organism produces a narrow zone of beta hemolysis on blood agar, is catalase positive, and exhibits characteristic "tumbling" motility in wet-mount preparations incubated at room temperature (3). In the United States, meningitis accounts for more than 75% of all infections caused by this organism (4). There is an increasing incidence of Listeria infection in immunosuppressed patients (2, 5, 7).

Antimicrobial agents used in treating Listeria infection include tetracycline, penicillin, ampicillin, erythromycin and chloramphenicol (8, 11). Synergistic antimicrobial combinations against sundry strains of *Listeria monocytogenes* have been described (12, 16). There is no generally accepted bactericidal agent recommended for penicillin allergic patients.

Trimethoprim-sulfamethoxazole is bactericidal for susceptible organisms and oral administration yields high cerebrospinal fluid concentrations (17, 19). We present two patients with *Listeria monocytogenes* bacteremia, one with proved meningitis, successfully treated with oral trimethoprim-sulfamethoxazole.

Case Reports

Case 1: A 53-year-old woman was admitted to The Mount Sinai Hospital with three days of malaise, headache, and fever. Systemic lupus erythematosus was diagnosed eight years before and the patient was treated with 12.5 mg prednisone per day. Physical examination on admission showed a confused, but alert, patient with a rectal temperature of 102.8°F. There was no nuchal rigidity but the patient did have slight left facial drooping, slight left arm weakness, urinary incontinence and a macular papular rash on the upper chest.

The white blood cell count (WBC) was 13,900/mm^3 with a predominance of polymorphonuclear neutrophils (PMN); venous hematocrit (Hct), 40%; and erythrocyte sedimentation rate (ESR, Westergren), 50 mm/hr. Lumbar puncture revealed clear fluid with an opening pressure of 215 mm H_2O; WBC, 439 with 96% PMN, 4% lymphocytes and no red blood cells (rbc). Cerebrospinal fluid (CSF) protein was 104 mg/dl; CSF glucose was 49 mg/dl with a blood glucose of 179 mg/dl. Gram stain of CSF showed no bacteria. Blood cultures taken on admission grew *Listeria monocytogenes* but cultures of CSF were negative. Because of a history of severe penicillin allergy, the patient was treated with intravenous chloramphenicol, to which the isolate was suscep-

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tible, at a dose of one gram every six hours; the prednisone dosage was increased. Within two days, the patient defervesced and all the neurologic abnormalities cleared. Lumbar puncture, four days after therapy was initiated, showed 20 WBC/mm^3 with 13% PMN and 87% lymphocytes; the glucose was 61 and protein 60 mg/dl. Chloramphenicol was discontinued after ten days. Two days later, she developed fever (103°F) with shaking chills and severe headache. CSF contained 450 WBC/mm^3 with 85% PMN and 15% lymphocytes. Blood and CSF cultures grew *Listeria monocytogenes*. She again was treated with intravenous chloramphenicol, one gram every four hours; prednisone dosage was tapered. Chloramphenicol was discontinued after 13 days because the patient developed thrombocytopenia and leukopenia. Within four days, she again developed fever, headache and chills. Lumbar puncture showed recurrence of meningitis and both blood and CSF grew *Listeria monocytogenes*. This time she was treated with oral trimethoprim (80 mg)-sulfamethoxazole (400 mg) (Table I), three tablets given every eight hours for three weeks. All symptoms abated and both blood and CSF were sterilized. The patient was ambulatory in the hospital during therapy. She has remained well, without recurrence of infection six months after therapy.

Case 2: A 32-year-old woman was seen as an outpatient on August 19, 1980 with complaints of fever and severe headache. The patient had hypothyroidism for twelve years treated with 0.3 mg sodium levothyroxine. She became pregnant in June of 1980. On August 12, 1980 she had a shaking chill with oral temperature of 102°F. The next day she noted scant vaginal bleeding. Fever and shaking chills continued; she developed abdominal cramps and passed blood clots vaginally. On August 15, 1980 the patient was admitted to The Mount Sinai Hospital for uterine suction curettage. She was treated with intravenous cefazolin, one gram every six hours. She was discharged three days later on 500 mg cephalexin every six hours. The day after discharge she noted fever to 101.5°F. When examined that evening she complained of severe frontal headache and a scant, now foul-smelling vaginal discharge. On physical examination the oral temperature was 101.5°F; blood pressure, 110/70/mmHg; pulse, 118/min; and respirations, 16/min. The neck was supple and the lung fields were clear on auscultation. There was a grade I/VI pulmonic systolic murmur. No abdominal masses were palpated. The hands and arms were quite cold and clammy. Laboratory data included WBC, 11,300/mm^3 with 61% neutrophils, 14% band forms, 15% lymphocytes and 10% monocytes; Hgb, 12.8 mg/dl; Hct, 35.5%; and ESR, 36 mm/hr.

Cervical cultures, abortus tissue cultures, as well as blood cultures done during hospitalization four days previously all grew *Listeria monocytogenes* susceptible to trimethoprim-sulfamethoxazole (Table I). The patient was warned of the possibility of meningitis and immediate admission to hospital was advised. However, the patient refused admission and after much discussion and consultation with the patient's private obstetrician, it was decided to treat her as an outpatient; the blood was again cultured. Because of a history of hives after oral penicillin several years previously, she was given a stat dose of four tablets of trimethoprim-sulfamethoxazole and told to take three tablets every eight hours. The patient and her husband, both of whom were quite reliable, were instructed to come to the hospital immediately if she experienced increasing chills, headache, stiff neck, somnolence, or vomiting. However, the following evening she felt well and was without fever. Trimethoprim-sulfamethoxazole therapy was continued for 14 days. The blood cultures taken prior to therapy again grew *Listeria monocytogenes* but blood cultures taken one week after therapy was completed were sterile. Five days after therapy was initiated the WBC was 8000/mm^3 with 56% neutrophils, 9% band forms, 30% lymphocytes, 3% monocytes, 1% eo-

TABLE I

Minimal Inhibitory (MIC) and Bactericidal (MBC) Concentrations of Antimicrobial Agents for Isolates of Listeria monocytogenes

Case 1

Agent	MIC (μg/ml)	MBC (μg/ml)
Tetracycline	0.31	<20
Tobramycin	2.5	10
Gentamicin	1.25	10
Erythromycin	<0.01	20
Rifampin	0.04	<5
Trimethoprim-sulfamethoxazole	<0.08	0.16
Chloramphenicol	(susceptible by disc assay)	

Case 2

Agent	MIC (μg/ml)	MBC (μg/ml)
Ampicillin	0.31	1.25
Cephalothin	2.5	5
Gentamicin	1.25	10
Chloramphenicol	5	<20
Erythromycin	<0.15	<20
Trimethoprim-sulfamethoxazole	5	—

sinophils and 1% basophils. The patient has remained well since therapy was completed.

Discussion

Trimethoprim-sulfamethoxazole has a wide spectrum of activity against a variety of microorganisms (20). The drug inhibits bacterial thymidine synthesis by blocking synthesis of the metabolically active form of folic acid, tetrahydrofolic acid (20). Both trimethoprim and sulfamethoxazole are well absorbed from the gastrointestinal tract, and penetrate the blood-brain barrier in meningitis to achieve therapeutic concentrations in cerebrospinal fluid (19, 20).

Our first patient had systemic lupus erythematosus. Listeria meningitis in a patient with systemic lupus erythematosus has been reported only once previously (2). Our patient relapsed twice despite intravenous chloramphenicol therapy; relapse has been reported with chloramphenicol as well as ampicillin or penicillin (2, 21). After three weeks of oral trimethoprim-sulfamethoxazole, she was discharged and has not subsequently relapsed. The second patient illustrated the well-documented association between listeriosis and pregnancy (3, 22). Relief of symptoms and fever was dramatic with oral trimethoprim-sulfamethoxazole and bacteriologic cure without relapse was achieved.

The minimal inhibitory (MIC) and minimal bactericidal concentrations (MBC) for the isolates from our patients were determined by the standard tube dilution method; all assays were performed in Mueller-Hinton broth using an inoculum of 10^6 to 10^7 colony forming units (cfu). Winslow (18), using a microtiter broth-dilution system, showed that all his clinical isolates of *Listeria monocytogenes* were susceptible to trimethoprim-sulfamethoxazole. However, the bactericidal effect was reduced when the inoculum size was increased from 10^4 cfu/ml to 10^5-10^6 cfu/ml (18). Wiggins et al. (23) found that results of in vitro tests with ampicillin, penicillin, erythromycin, and tetracycline were greatly influenced by the methodology, including inoculum size, media, and the definitions used for end points. Therefore, it is difficult to predict clinical response of *Listeria monocytogenes* infections to therapy based on laboratory antibiotic susceptibility tests.

Listeria monocytogenes is an intracellular parasite that can survive and multiply in the reticuloendothelial system of the hosts (1, 3, 7, 24, 25). The organism penetrates corneal, conjunctival, urinary bladder, HeLa and small intestinal epithelial cells. Fowle (26) has presented evidence for the penetration of trimethoprim into intracellular fluid at concentrations higher than those in plasma; intracellular labelled trimethoprim has also been detected in various bacteria (26). On the other hand, tissue levels of sulfamethoxazole are not very high and substantial amounts do not penetrate intracellular fluids (26). It is also of interest that trimethoprim-sulfamethoxazole has been useful in the treatment of other intracellular bacterial infections such as brucellosis and typhoid fever (27, 29); the effectiveness of the drug in combination in our patients may have been related in part to the intracellular penetrance of trimethoprim.

The use of oral trimethoprim-sulfamethoxazole for the treatment of infection due to *Listeria monocytogenes* has not been previously reported. We have demonstrated that the drug combination can be used in penicillin-allergic patients for the ambulatory treatment of both bacteremia and meningitis. Since the incidence of listeriosis is increasing, especially in immunosuppressed patients, more studies with trimethoprim-sulfamethoxazole on a larger number of patients with listeriosis are warranted. We also suggest that responsible bacteremic patients can be treated as outpatients when effective, well-absorbed and distributed, oral antimicrobial agents are available. This may be especially significant in this era of rapidly rising costs of hospitalization.

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Prevention of Ischemic Renal Damage with Prostacyclin

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Introduction

Ischemic damage during kidney retrieval remains a major problem in clinical transplantation. Treatment to prevent or minimize the ischemia is critical for successful transplantation. Prostacyclin (PGI_2) is a prostaglandin that induces vasodilatation and prevents aggregation of platelets. These pharmacologic effects suggest that this agent may be useful in the prevention of ischemic damage.

Among the several recent reports regarding PGI_2 and acute tubular necrosis (ATN), most notable is the work by Mundy et al (1). These investigators utilized unilaterally nephrectomized dogs whose remaining kidney had received 45 minutes of warm ischemia and PGI_2 infusion prior to autotransplantation. The treatment resulted in a marked increase in renal blood flow and an associated drop in renal vascular resistance along with a return to normal kidney function within 48 hours posttransplantation. Hill and Moncada (2) demonstrated that the beneficial effects of PGI_2 were indeed due to the exogenous administration of PGI_2 and not an endogenous secretion of one of the prostaglandins. With regard to the mechanism of PGI_2's effect on solute excretion, while one school suggests a direct tubular interaction (3), others postulate indirect changes in reabsorption caused by strictly vascular phenomenon (4). Regardless of the remaining controversies, a substantial portion of the literature supports the possible benefits of PGI_2 not only in kidney transplantation but in transplantation of other organs, the treatment of hypercoagulopathy seen in acute myocardial infarction or diffuse intravascular coagulopathy, and in extra corporeal circulation systems such as hemodialysis (5).

In a previous investigation, we found that PGI_2 and Tris Buffer administered in a volume of 1 ml were equipotent in their ability to prevent ischemic ATN (6). The present work was designed to eliminate the effects of volume and thereby provide a basis for the determination of the efficacy of PGI_2 in protecting the kidney from ischemic damage.

Materials and Methods

Rats: Male Sprague-Dawley rats weighing approximately 250 grams were used throughout the experiments.

Operative Procedure

All animals were anesthetized with ether inhalation. The abdomen was shaved, the skin wiped with ethanol and the animals were placed in four-limb restrainers. A midline incision was made from 2 cm below the xiphoid process to just above the pubis. The abdominal contents were reflected to expose the right kidney which was removed. The left kidney was exposed and the renal artery and vein were isolated. Silk (6-0) was placed around each vessel in loop formation in preparation for occlusion. The renal artery was injected with either Tris Buffer or PGI_2 (0.5 ml) using a 30-gauge steel hypodermic needle. The renal artery and vein were immediately occluded for 90 minutes by tightening the silk loops. During the ischemic period, the peritoneum was kept moist with normal saline soaks containing penicillin. At the end of the ischemic period, the ligatures were released and the abdomen was closed. The animals were placed under a heat lamp for ten minutes and returned to metabolic cages. Daily BUN levels were measured for five postoperative days.

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FIGURE 1

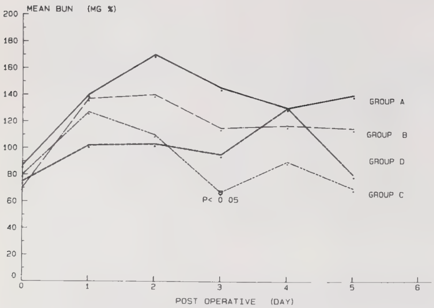

FIG. 1. This figure shows the mean BUN levels of the four groups during the first five days postischemia. The animals that received PGI_2 2 mcg/ml show a decreased BUN level significant at day three when compared with controls.

BUN Determinations

A Beckman BUN analyzer was utilized for BUN determinations. Blood samples were obtained from the rat tails.

PGI_2 Solution Preparation

PGI_2 was prepared in a Tris Buffer at pH 9 every 48 hours and kept at 4°C.

Experimental Design

The experimental animals were divided into four groups of five to eight rats each. Group A received no treatment prior to occlusion. Group B received a 0.5 ml injection of Tris Buffer just prior to the renal pedicle occlusion; Group C received PGI_2, 2 micrograms per ml in 0.5 ml; Group D was injected with PGI_2, 5 micrograms per ml in the same volume. All rats were fed water and rat chow ad lib.

Statistics

Statistical analyses were performed using the Student's t-test.

Results (Figure 1, Table I)

The control (Group A) represented the experimentally-induced ATN. The BUN peaked on day 2 to 170 mg% and remained elevated for five days showing a slow decline towards baseline. The BUN values of the group receiving 0.5 ml buffer mirrored those of the control without any significant difference. Group C, which received 0.5 ml of a solution of 2 micrograms per ml of PGI_2 showed a mean BUN lower than the control and animals with buffer alone, every day with a statistically significant difference on day three ($p < 0.05$). Group D which received 0.5 ml of a solution of 5 micrograms per ml PGI_2 also had lower BUN's on all days. However, it did not demonstrate any significant difference from the controls.

Discussion

Our initial investigation established that given a sufficient volume of either Tris Buffer or PGI_2, adequate protection from ischemic ATN could be achieved (6). The present experiment demonstrated that 0.5 ml of Tris Buffer (one-half the original volume) did not produce the same protective effect. These results highlight the effect of volume on the protection of ischemic damage demonstrated in our previous work. The elimination of the volume effect allowed the determination of the effectiveness of PGI_2. The findings indicate a mild degree of protection from PGI_2. Although the trend of the results obtained with the high dose of PGI_2 suggested a similar effect, the results did not achieve statistical significance. In view of Prostacyclin's pharmacologic properties, one would have expected a more profound effect. Statistically, the lower dose was more effective. The results of this study suggest a beneficial effect of PGI_2 in the prevention of ischemic ATN.

Summary

The present work studied the effect of Prostacyclin (PGI_2), a prostaglandin with vasodilator

TABLE I
Mean Bun Values

Group	N	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5
Control	8	87 ± 44	140 ± 34	170 ± 113	144 ± 113	131 ± 104	141 ± 143
Buffer 0.5 ml	5	69 ± 29	139 ± 35	140 ± 73	115 ± 41	96 ± 14	117 ± 107
PGI_2 2 mcg/ml 0.5 ml	5	81 ± 36	128 ± 60	109 ± 45	67 ± 32*	90 ± 69	68 ± 13
PGI_2 5 mcg/ml 0.5 ml	5	72 ± 13	101 ± 23	102 ± 47	95 ± 43	137 ± 70	79 ± 60

* $p < 0.05$ as compared with control

and platelet antiaggregating characteristics, in the prevention of ischemic acute tubular necrosis (ATN). Ischemia was produced in uninephrectomized Sprague-Dawley rats by occluding the renal pedicle for 90 minutes. Renal function was determined by serum BUN measurements daily for 5 days. Solutions to be tested were injected in the renal artery at the time of occlusion. Four groups of rats were done: Group A, control (not treated); Group B, Buffer 0.5 ml; Group C, PGI_2 2 mcg/ml in 0.5 ml; Group D, PGI_2 5 mcg/ml in same volume. PGI_2 at 2 mcg/ml administered in 0.5 ml produced protection of ischemic damage at all days, significant to $p < 0.05$ at day 3, whereas Buffer alone or PGI_2 at 5 mcg/ml injected in the same volume did not show this effect. The results of this study suggest a mild beneficial effect of PGI_2 in the prevention of ischemic ATN.

Acknowledgments

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Is a Gastric Drainage Procedure Necessary after Proximal Gastrectomy or Esophagogastrectomy and Esophagogastrostomy?

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Abstract

A gastric drainage procedure seems to be necessary with the esophagogastrostomy because of the inevitable incidental bilateral truncal vegotomy which occurs during the proximal gastrectomy of an esophagogastrectomy for carcinoma of the cardia, fundus, or lower esophagus.

Although limited evidence favors gastric drainage in such conditions, there is some clinical and experimental work that indicates excellent results when such a drainage procedure is avoided.

During a seven-year period, 14 patients were submitted to an esophagogastrectomy for carcinoma of the gastroesophageal junction with restoration of the gastrointestinal continuity by an esophagogastrostomy without a drainage.

Evaluation of our patients at three different time intervals after the operation with clinical assessment, radiologic, and endoscopic examinations indicated that drainage was not necessary and that the majority of the patients were symptom free with no evidence of gastric retention or any problem of gastric emptying.

Bilateral truncal vagotomy should be considered inevitable during proximal gastrectomy or esophagogastrectomy for carcinoma of the cardia, fundus or lower esophagus. In addition, since Dragstedt and Shafer in 1945 clearly defined the complications of vagotomy without drainage, it has been complemented by gastric drainage.

For years, the Heineke-Mikulicz pyloroplasty, with the Ramstedt pyloromyotomy as an adequate alternative, have been the answer for the expected stasis in the gastric remnant (antrum) when the latter was anastomosed with the proximal esophagus. However, over the last two decades there have been reports in the literature both from clinical (Angorn, 1975; Collis, 1971; Ellis, F. H., 1980; Logan, 1963; Zacho et al, 1965) and experimental data (Shapiro et al, 1972) that show such a pyloroplasty is probably unnecessary.

This is a retrospective study of a limited number of our patients in whom gastrointestinal continuity following esophagogastrectomy for carcinoma of the gastroesophageal junction was restored by esophagogastrostomy without a pyloroplasty.

Patients and Methods

During the years 1971 to 1978, 14 patients with carcinoma of the gastroesophageal junction were submitted to esophagogastrectomy followed by esophagogastrostomy without pyloroplasty. The anastomosis had been an end-to-side on the anterior gastric wall in one layer continuous dexon 2.0 reinforced by two silk 2.0 stay sutures at the corners (Fig. 1).

There were ten males with age ranging from 52 to 73 years (mean age 64.6) and four females with age ranging from 56 to 71 years (mean age 62.4).

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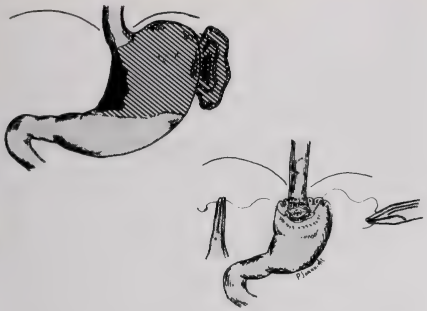

FIG. 1. One layer end-to-side esophago-gastro anastomosis on the anterior wall of the gastric remnant following esophagogastrectomy without drainage.

There was no operative mortality. The patients were evaluated at three and twelve months after the operation and also recently three to nine years postoperatively. Evaluation included only clinical assessment at the first interview, while radiologic and endoscopic examination was performed at subsequent follow-up.

Results

At the three-month period, all patients seemed to be well. There was no clinical evidence of gastric stasis. Nine patients had no symptoms. Three patients complained of fullness, and were advised to change the rate and type of meals to more frequent and smaller. Two patients had mild diarrhea.

At 12-month follow-up, only 11 patients were evaluated. There was one unrelated death and two deaths from disseminated disease. On clinical assessment, nine of the 11 patients were symptom-free.

One patient was suffering from mild diarrhea and one was regurgitating when lying flat. There was no dysphagia, fullness, dumping or vomiting.

On endoscopy, there was no obvious bile reflux through the intact pylorus. Seven of the 11 patients examined showed evidence of atrophic gastritis (grade III−IV) consisting with the age on biopsies of the distal antrum. Mucosa of the distal esophagus was normal in all but two of the patients (one complained of regurgitation) in whom mild esophagitis was noticed, and confirmed on biopsies. Emptying of the stomach seemed to be within normal limits in all patients on radiologic examination after a standard meal with 50ml of Barium. Barium entered the duodenum within the first few minutes after the patients swallowed the contrast (Fig. 2). All stomachs were empty from any contrast within six hours after the onset of the examination.

Six patients, surviving three to nine years after the operation, were examined recently. All patients were symptom-free at clinical evaluation. Endoscopy and biopsies of the prepyloric antrum revealed moderate to severe atrophic gastritis to all of them, while four of them showed mild to morderate esophagitis on biopsies of the distal esophagus.

Radiologic examination showed no evidence of gastric retention or any problem in gastric emptying.

Discussion

Standard surgical technique of esophagogastrostomy following esophagogastrectomy, is combined with a gastric drainage procedure because of the invariable parasympathetic gastric denervation following any operation in which the lower esophagus is resected (Dermond, 1976: Ellis H., 1976). In fact there is very little evidence that such a procedure is really necessary. On the con-

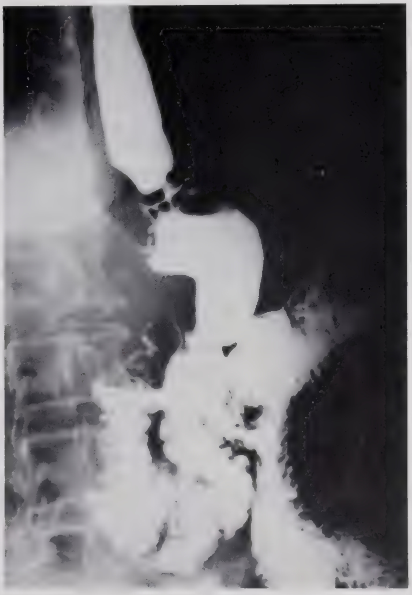

FIG. 2. Radiologic examination 12 months after an esophagogastrectomy with an esophagogastrostomy without a pyloroplasty. Gastric emptying begins within few minutes after swallowing the contrast medium.

trary, the work of Zacho and Fischermann based on 86 patients clearly showed that such a procedure is unnecessary as the vast majority of patients did very well without it.

This concept was reinforced seven years later by the experimental work of Shapiro whose studies of gastric emptying on 12 mongrel dogs which had undergone vagotomy and esophagogastrostomy with and without pyloroplasty showed no difference between the two groups, thus proving that a gastric drainage procedure was unnecessary. In 1975 Angorn reviews excellent results from ten of his patients in whom gastric drainage was not performed, and recently Ellis concludes from the review of 27 out of 72 patients who did not have a gastric drainage that such a procedure is not always necessary (Ellis et al, 1979). Postoperative retention was noticed in only three patients who were subsequently submitted to a pyloroplasty.

The results of our small series clearly indicate that at least to some of these patients, gastric drainage is unnecessary after esophagogastrectomy and esophagogastrostomy. None of the few clinical complaints could be attributed to the lack of such drainage. Fullness should be attributed to the decreased capacity of the gastric reservoir and regurgitation to the absence of the L.E.S.

The endoscopic findings are not different from those observed in matched groups of patients with similar operations and from the radiologic damaging the pyloric sphincter are obviously avoided (that is, immediate postoperative complications dumping, bile reflux) and, according to Ellis and Gibb, it is very doubtful whether gastric drainage influences the anastomotic integrity. What would the reason be for the adequate emp- studies, gastric retention with stasis could be excluded.

In addition, all the problems that can arise by tying of the antrum in those cases of vagotomy without drainage? Apart from the possible activation of the independent antrum's pacesetter potential (Shapiro et al, 1972) one could think of the beneficial influence that the change of the antrum's position that allows gravity to play a more significant role in the gastric emptying.

Finally, if one believes that some patients will develop retention at the end and will demand a gastric drainage (Ellis et al, 1979), the establishment of the criteria for those who will need a pyloroplasty seems mandatory so that these patients can have their drainage procedure at the first stage.

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Tuberculous Ileotyphlitis with Formation of Large Ileal Pseudopolyp Mimicking Tumor*

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Abstract

A 26-year-old woman presented with weight loss, weakness, nocturnal diaphoresis and abdominal pain. She had direct tenderness in the right lower abdominal quadrant. The P.P.D. test was negative. X-ray revealed ulceration and erosion of the ileal, cecal and ascending colonic mucosa, with a large filling defect in the terminal ileum. The surgical specimen contained a large inflammatory pseudopolyp in the terminal ileum. Cultures of the intestinal wall and lungs grew Mycobacterium tuberculosis.

Formation of inflammatory pseudopolyps in secondary tuberculosis of the colon is well known (1). However, this has not been described in the ileum; we present such a case.

Case Report

A 26-year-old woman, born in eastern Europe, but in the United States for 24 years, had symptoms of weight loss (7-8 kg) during the two months preceding admission, as well as weakness, nocturnal diaphoresis, abdominal pain, anorexia and mild diarrhea. The abdominal complaints started approximately five months prior to admission, and were initially vague, diffuse, and cramp like. Later the pain localized in the right lower abdominal quadrant. Five days prior to admission, she had a few episodes of loose stools. Two months prior to admission, the patient developed weakness and easy fatigability, which severely increased in intensity over the three weeks preceding admission. A 10-month-old daughter was delivered in a cesarean section. She was not aware of having received antituberculous vaccination (B.C.G.). Four years prior to admission, she had a negative P.P.D. test. However, it was found to be positive two years later; antituberculous therapy was suggested, but refused by the patient.

She was pale, had a pulse of 120-140/minute, blood pressure of 75/100-110 mm Hg and temperature of 102-103° F orally. There were no findings on physical examination of the chest. There was no hepatosplenomegaly or lymphadenopathy, but the abdomen was distended. Palpation revealed fullness and, possibly, a mass in the right lower abdominal quadrant; there was mild direct tenderness in this area, without rebound tenderness and muscle guarding. The P.P.D. test performed on this admission was negative.

The erythrocyte sedimentation rate was 68 mm/hour. There was hypochromic microcytic anemia, with a hemoglobin level of 9-10 gm%, and serum iron determination of 20 microgm%, with concomitant low serum iron binding capacity. The bone marrow showed increased iron content. Serum vitamin B12 level was normal. The peripheral white cell count was 7,600/cu mm (54% segmented neutrophils, 15% bands, 23% lymphocytes, 6% monocytes, 2% basophils). The platelet count was 450,000/cu mm. Serum albumin determination was 3.7 gm%, with a total serum protein of 6.6 gm%. The stools were guaiac test negative.

The chest x-ray was unremarkable. Abdominal x-ray, after barium meal, as well as barium enema, revealed severe abnormality of the terminal 20-25 cm of the ileum. There was persistent

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* This case was presented by Karl O. Schwarz, M.D., on June 11, 1981 at the weekly surgical pathology conference of The Lillian and Henry M. Stratton-Hans Popper Department of Pathology, The Mount Sinai Medical Center, New York.

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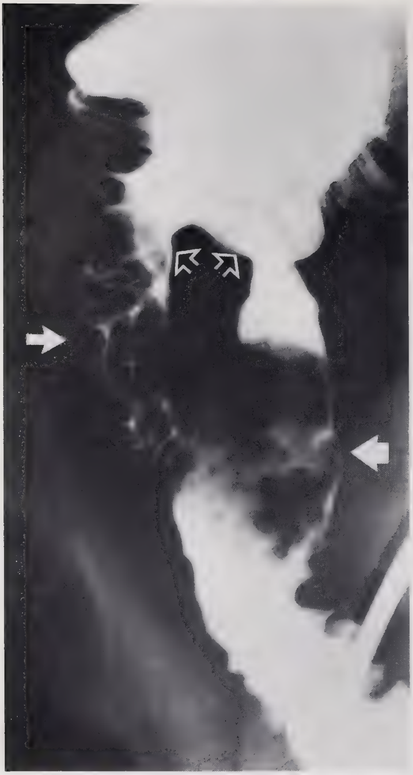

FIG. 1. Spot x-ray of the ileocecal region from barium enema. The cecum is persistently nondistensible with thickened mucosal folds (small arrow). Mucosal effacement suggestive of ulceration is seen at the ileocecal junction (open arrows). A large intraluminal filling defect expands the lumen of the distal ileum without evidence of obstruction (large arrow). Proximally, the ileal mucosal folds are thickened. The entire ileocecal region appears encased by a mass.

irregular narrowing of the lumen, rigidity of the wall with thickening of the mucosal folds and extensive ulceration, extending into the cecum and proximal ascending colon. A large filling defect, with irregular lobulated surface, projected into the lumen. The barium enema also showed encasement by mass of the entire ileocecal region (Fig. 1). Sonography demonstrated a 6.0 × 2.8 × 5.0 cm mass, with a strongly echogenic center in the right lower abdominal quadrant. The sonographic image was interpreted as inflamed terminal ileum and cecum with abscess formation.

The terminal ileum, cecum and most of the ascending colon were resected. The surgical specimen showed multiple fibrous adhesions. The ileal mesentery and the ileocecal and proximal ascending colonic serosa showed multiple, partly confluent, white-gray nodules (Fig. 2); histologically these were caseating granulomata. There was mesenteric lymphadenitis with caseating granulomata. The terminal 35 cm of the ileum had a rigid, thickened 1.5 cm wall, and there were multiple annular 3–5 cm long ulcers; the intervening mucosa was severely edematous with thickening of the valvulae conniventes Kerckringi. The ileal wall was extensively infiltrated by multiple, confluent granulomata, with extensive destruction of the tunica muscularis externa (Fig. 3). The terminal 8 cm of the ileum was extensively ulcerated and nodular. There was a 3 cm, purple, polypoid mass, 5 cm proximal to the ileocecal valve, and it had a 0.8 cm long stalk (Fig. 4). The polyp consisted of confluent granulomata with Langhans giant cells and scant granulation and connective tissue. The ulceration stopped sharply at the ileocecal valve. Large areas of erosion were scattered in the cecum and proximal ascending colon; however, the large intestinal wall, with the exception of the vermiform appendix, was not thickened. The vermiform appendix had a pinpoint lumen; its wall was rigid and 0.8 cm thick; the covering serosa showed multiple, small nodules.

Confluent caseating granulomata with Langhans giant cells were demonstrated in the ileal, cecal and colonic walls and serosa, in the ileal pseudopolyp, in the ileal mesentery and mesenteric lymph nodes and in the vermiform appendix and mesoappendix. Smears from the resected intestinal segment, as well as examination of histologic sections from all of the above mentioned areas showed acid-fast bacilli in abundance (Fig. 5).

Cultures from the intestinal wall, as well as sputum cultures, grew Mycobacterium tuberculosis (old name: Mycobacterium tuberculosis var. hominis).

Discussion

Formation of large pseudopolyps in secondary tuberculosis of the large bowel is well known (1, 2). However, a large tuberculous pseudopolyp in the terminal ileum has not previously been described (3, 4).

Ileocecal tuberculosis may mimic neoplasia or Crohn's disease (4, 5); this case is a good illustration of that. Despite that ileocecal tuberculosis is

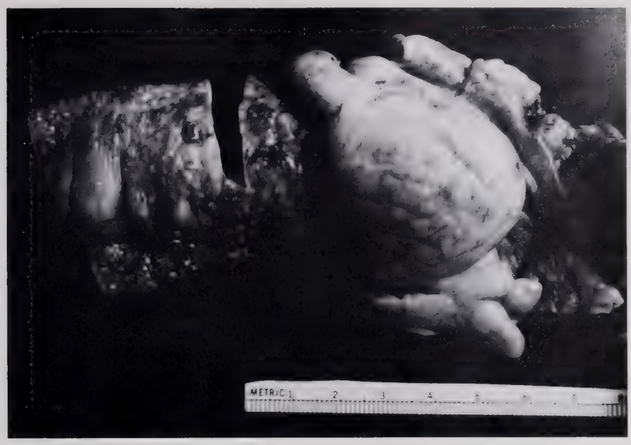

FIG. 2 Multiple, partly confluent, white-gray nodules in the ileocecal and proximal ascending colonic serosa.

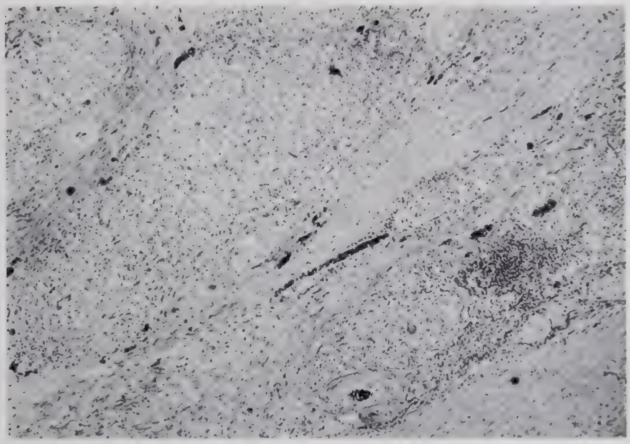

FIG. 3 Photomicrograph of the ileal wall showing multiple, confluent granulomata, infiltrating the tunica muscularis externa, and causing its destruction (hematoxylin-eosin stain, original magnification ×40).

the rarest among the above mentioned disorders, it nevertheless deserves to be considered as the first diagnosis to be confirmed or excluded. The evaluation of patients presenting with vague symptoms pertaining to the ileocecal region, should include chest x-ray and sputum and feces culture for Mycobacterium tuberculosis. The reason for this is, of course, the relatively easy curability of the disorder, and the severe outcome when the diagnosis is delayed. Indeed, the outcome is catastrophic when corticosteroid treatment is attempted. Localized giant pseudopolyposis may also develop in ulcerative or granulomatous (Crohn's) colitis. The initial recognition is largely dependent on barium enema examination; the diagnosis should be suspected whenever a villous-like or multinodular polypoid mass develops in a patient with known colitis, or when

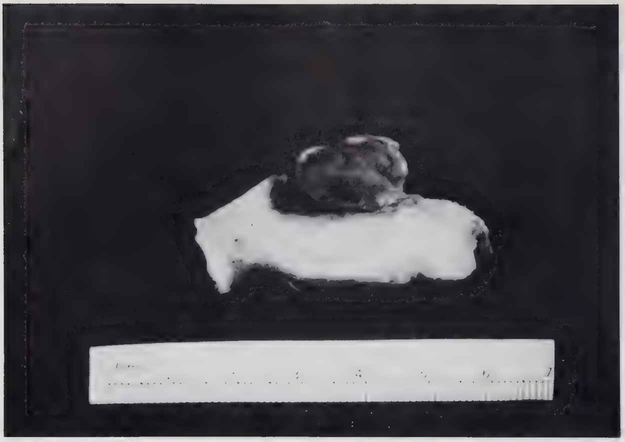

FIG. 4 Pedunculated, polypoid mass in the terminal ileal lumen; the intestinal wall is greatly thickened.

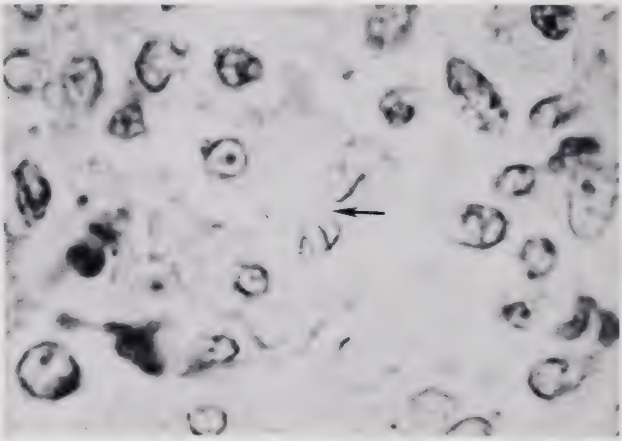

FIG. 5 Photomicrograph of the ileal wall; the arrow points at acid-fast bacilli (Ziehl-Neelsen's carbolfuchsin staining method, original magnification ×1000).

such an intraluminal mass is seen in association with radiographic changes of diffuse or segmental inflammatory disease elsewhere in the colon (6). Anamnestic or radiologic evidence of existing ulcerative or granulomatous colitis is of paramount importance in differentiating these conditions from ileocecal tuberculosis.

Our case had extensive destruction of the muscularis externa of the terminal ileum. It is interesting that this was accompanied by only minimal symptoms. The therapeutic approach for ileocecal tuberculosis should be in two phases. First, a medical cure should be attempted. If, however, a paralytic intestinal segment develops due to destruction of the muscularis externa, or if obstruction develops due to cicatriceal stenosis or occluding inflammatory pseudopolyp, then segmental intestinal resection is the inevitable choice of therapy.

In our case the symptomatic tuberculous infection developed in close temporal proximity to pregnancy. It is known that pregnancy is a physiologic state of decreased immunologic resistance (7); this could have played a role in the present case. However, it is interesting to note that in the older medical literature, pregnancy was thought to have a most beneficial effect on the prognosis of tuberculosis (8).

Acknowledgments

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Gastric Hamartomatous Polyps in the Absence of Familial Polyposis: Report of Two Cases

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Abstract

Two cases of polypoid hamartoma of the stomach in the absence of familial polyposis are presented. There are no previously reported cases of isolated, symptomatic gastric hamartomas. The benignity of this condition should be emphasized. Local excision is curative.

Gastric hamartomatous polyps have been described with Peutz Jeughers, Gardners and Cronkhite-Canada syndromes (1–4). The clinical presentation of isolated gastric hamartomatous polyps has not been previously reported. We report two such cases, treated recently at The Mount Sinai Hospital, New York.

Case Reports

Case 1

An 85-year-old white female was admitted to The Mount Sinai Hospital in November of 1979 with a history of several days of nausea, vomiting and abdominal pain. She was well until one year prior to admission, when she began having epigastric pain, occasional postprandial vomiting and 8 pounds weight loss. There was no family history of gastrointestinal or pigmentary disorder.

Physical examination on admission revealed a thin, pale female. There were no perioral pigmentations of subcutaneous soft tissue tumors. Examination of the abdomen revealed a distended epigastrium with a palpable nontender mass in the right upper quadrant measuring 4 cm in diameter. A succussion splash was present.

Significant laboratory data on admission: hematocrit 25% (M.C.V. 74mm^3). W.B.C. 9.000, S.M.A. 6 was normal; S.M.A. 12 revealed a protein of 4.8 g% and albumin 2.8 g%. Barium enema and sigmoidoscopy prior to admission were normal. Admission abdominal x-rays showed a distended, fluid and air filled stomach.

In the hospital, she was drained of large volumes of nonbilious fluid through a nasogastric tube. Upper gastrointestinal series demonstrated an irregular polypoid lesion in the mid and distal antrum which was intussuscepted into the first, second and third portions of the duodenum, obliterating its normal landmarks and producing partial obstruction of the gastric outlet (Figs. 1, 2).

At laparotomy, a fungating polypoid mass measuring 7 cm in diameter was palpated in the descending duodenum. It was easily reduced into the stomach with the base of the mass located in the anterior wall and greater curvature of the antrum. The remaining stomach and the rest of the abdominal contents were normal. A wedge resection of the involved stomach was performed.

Pathologic examination of the specimen revealed a segment of stomach measuring 5 by 11 cm. The mucosal surface was almost completely replaced by a fungating polypoid mass (Fig. 3). The polyps were pinkish yellow in color and soft in consistency. The serosa of the stomach was smooth and normal.

Microscopy revealed lobules with hyperplastic mucous cells in the surface and normal appearing glands in the center. Bundles of smooth muscle were present communicating with the muscularis mucosa and extending between the glands. These features were interpreted as gastric hamartoma.

Her postoperative course was uneventful and

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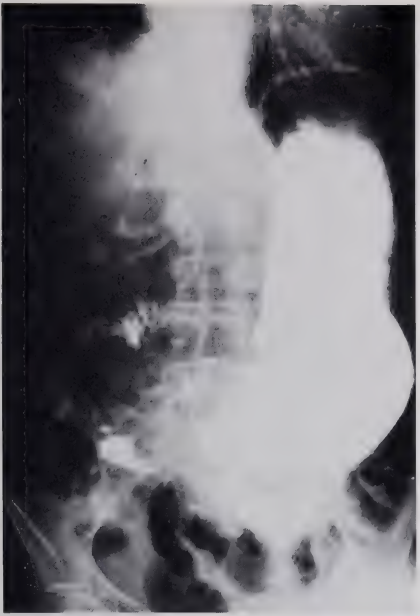

FIG. 1. Upper gastrointestinal series. Tumor protruding into the duodenum producing obstruction of the stomach.

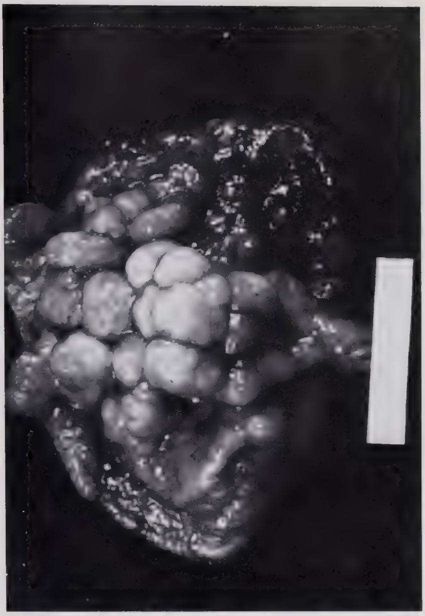

FIG. 3. Portion of distal stomach with soft polypoid tumor—portion of the stomach measures 5 × 11 cm.

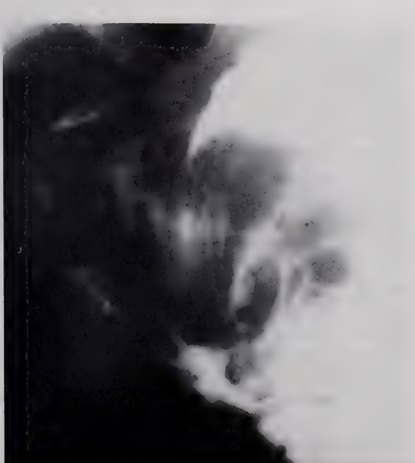

FIG. 2. Spot film showing tumor in the duodenum occluding the lumen—note the smooth polypoid surface of the tumor.

she was discharged well on the seventeenth postoperative day.

Case 2

A 51-year-old white female was admitted to The Mount Sinai Hospital in March, 1980 with the diagnosis of a small bowel tumor. She had been in good health until one week prior to admission when she had experienced mild epigastric discomfort followed by marked melena and a brief syncopal episode. She was admitted to another hospital with a hemoglobin of 5 g%. Upper gastrointestinal series revealed distortion of the distal duodenum and what was felt to be a submucosal lesion of the proximal jejunum (Fig. 4). She had no family history of gastrointestinal disease.

Physical examination revealed a healthy female. There were no abnormal pigmentations or subcutaneous lesions. Routine blood tests and liver scan were normal except for anemia. Barium enema was normal. She was transferred to The

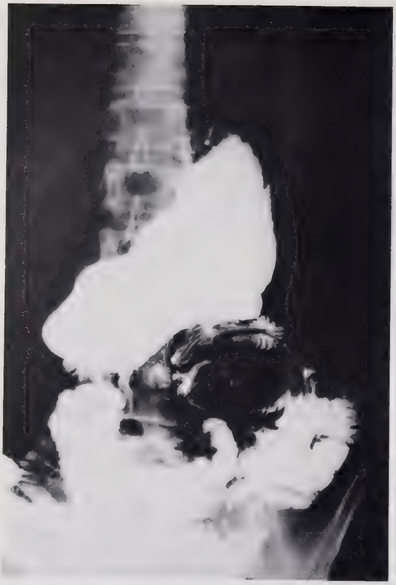

FIG. 4. Upper gastrointestinal series showing filling defect in proximal jejunum. The distal antrum and duodenum are distended.

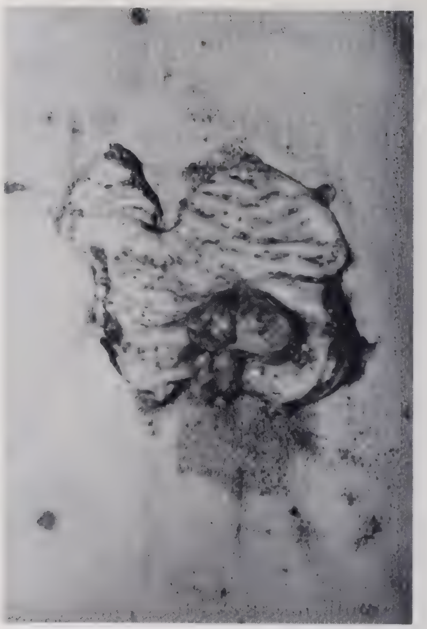

FIG. 5. Soft pedunculated tumor arising from distal antrum. The surrounding mucosa was normal.

Mount Sinai Hospital where she underwent laparotomy with the diagnosis of small bowel lymphoma.

At laparotomy the small bowel was normal. A soft pedunculated polyp arising from the distal antrum had intussuscepted into the proximal small bowel. Although the stalk was short, there was sufficient pliability of the adjacent tissues to intussuscept the polyp through the entire duodenum. A distal gastrectomy was performed.

Examination of the resected specimen revealed a soft polypoid fungating mass measuring 4 by 6 cms occupying the anterior wall of the stomach with a 2 cm stalk. The remaining gastric mucosa was normal. The overlying serosa was smooth and unremarkable (Fig. 5).

Microscopy revealed lobules with hyperplastic mucous cell in the surface and bundles of smooth muscle between the glands entering from the muscularis mucosa. These features were consistent with the diagnosis of gastric hamartoma (Figs. 6, 7).

Her postoperative course was uneventful and she was discharged well on the 10th postoperative day.

Discussion

Hamartomas are nonneoplastic formations in which tissues indigenous to that organ are abnormally intermixed, usually with a preponderance of one, or more than one type of tissue (2). Some hamartomas are gentically transmitted and a careful family history is always essential. Hamartomas are not uncommon in the gastrointestinal tract; the preponderant elements are connective tissue derivatives including nerve elements, vasoformative tissue, smooth muscle and lamina propria.

Hamartoma of the stomach not associated with the more commonly described syndromes (−) is a very rare entity. The first cases of gastric hamartomas in the absence of any of the above syndromes was reported by Tatsuta et al (5) as an incidental finding on routine surveillance gastroscopy.

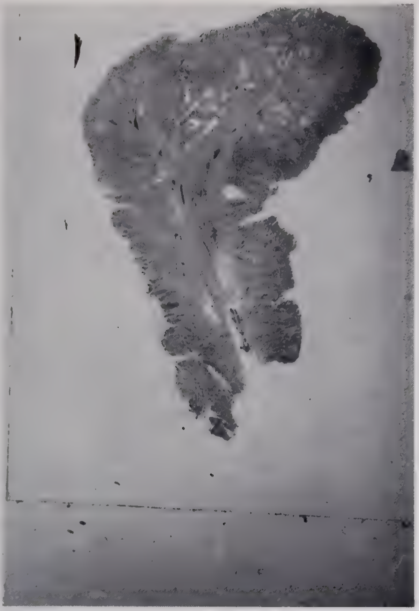

FIG. 6. Lobule of hyperplastic mucous cells with smooth muscle between the glands (Hematoxylin & Eosin ×100).

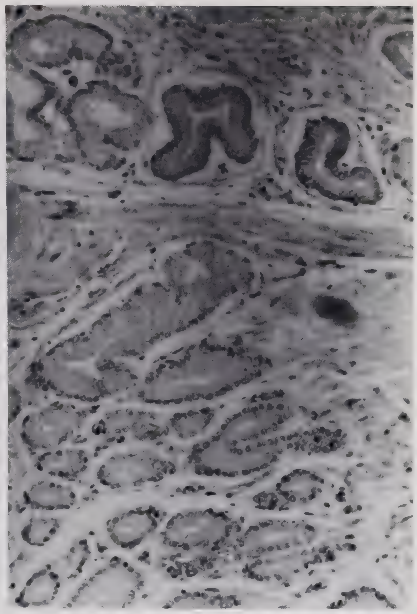

FIG. 7. Regular mucous cells with smooth muscle between the lobules (Hematoxylin & Eosin ×1000).

The histopathologic features of a gastric hamartoma are the presence of lobulated polyps with hyperplastic mucous cells on the surface and normal appearing gastric glands in the center. Bundles of smooth muscle extend from the muscularis mucosa at the base of the polyp into the lobules and between the glands (2).

Heterotopic adenomatous polyps of the stomach, also known as adenomyoma, lack prominent hyperplasia of the superficial mucosa and have normal appearing Brunners glands. These features differentiate them from gastric hamartoma.

Clinically these cases presented with obstruction (Case 1) and bleeding (Case 2). Because of the rarity of gastric hamartomas they may be mistaken for primary gastric malignancy.

The nonneoplastic nature of this disease indicates that a limited resection of the involved area should be undertaken when they become symptomatic or when the histopathology of the lesion is uncertain.

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Nitrous Oxide Anesthesia May Double the Balloon Gas Volume of Swan-Ganz Catheters

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Abstract

We studied the overdistension of Swan-Ganz catheter balloons that may result from exposure to N_2O. We surrounded balloons with saline equilibrated with 50% or 75% N_2O at 37° for ten-minute periods. When the inflating gas was air, the original balloon volume (1.5 ml) rapidly expanded by 65% and 96%, respectively, for the two levels of N_2O in the surrounding medium. Volume decreased 18% and 29% when the inflating gas was 50% or 75% N_2O, respectively. Volume decreased the most (49% and 38%, respectively, for the two levels of N_2O in the surrounding medium) when the inflating gas was 100% CO_2. Volume decreased only slightly when the balloon was inflated with air and exposed to saline equilibrated with air. We conclude that complications associated with overdistension of Swan-Ganz catheter balloons may be minimized by avoiding prolonged inflation of the balloon during N_2O anesthesia or by using CO_2 or N_2O as the inflating gas.

Introduction

Flow-directed pulmonary artery catheters may cause major complications including rupture of the pulmonary artery (1), pulmonary infarction (2), pulmonary artery-bronchial fistula (3), and rupture of the balloon (4). Indeed, over the past few years, the most common complication requiring emergency pulmonary resection to control massive hemoptysis at the Massachusetts General Hospital has been injury to the pulmonary artery caused by Swan-Ganz catheters (5). Overdistension of the balloon may be a contributing factor. Kaplan et al (6) demonstrated that overdistension occurs if the balloon is filled with air and placed in a gaseous atmosphere containing N_2O. Such expansion results because nitrous oxide diffuses into the balloon more rapidly than air diffuses out. We have extended those observations by using a surrounding medium of saline at 37° C (rather than a gas phase at room temperature), and by substituting CO_2 (as recommended by the manufacturers of the catheter) and N_2O as the inflating gas.

Materials and Methods

We used five Swan-Ganz catheters (Edwards Laboratories, Santa Ana, CA) for our studies. The balloon connection of each catheter was attached via a three-way stopcock to a saline-filled pressure transducer (Hewlett-Packard, Paramus, NJ) and a well lubricated 3 ml glass syringe. A blood warmer (McGaw, Glendale, CA) was filled with 0.9% saline and kept at 37°C. Mixtures of nitrous oxide and oxygen, oxygen alone or air alone were delivered at a 2 L/min flow from a Foregger anesthesia machine and were bubbled through the warmed saline prior to and throughout each study. The warmer was covered to keep the overlying atmosphere at the delivered gas concentration. The delivered concentration was monitored using a polarographic oxygen analyzer (North American Drager, Telford, PA). The catheter balloon was initially deflated to the point where the pressure in the system equalled zero. The catheter was placed in the saline and the balloon immediately inflated with 1.5 ml of air from the syringe. At 1-minute intervals, the balloon was deflated by withdrawing gas with the syringe until

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the system pressure read zero (atmospheric) pressure. The volume in the syringe was noted, and the gas was then immediately returned to the balloon. Measurements were made each minute for ten minutes, each measurement taking about ten seconds.

The balloon was first inflated with room air and exposed to saline equilibrated with N_2O at concentrations of 50% or 75% in oxygen. Then 50% or 75% N_2O was used as both the inflating gas and the gas in the saline. Next, 100% CO_2 was used to inflate the balloon, and the surrounding medium was 50% or 75% N_2O in saline. The study was repeated using air and then 100% CO_2 as the inflating gas, and air in the surrounding medium. Finally, air was used for inflation and 100% oxygen was used in the surrounding saline.

Results

When the balloon was inflated with air and exposed to nitrous oxide, balloon volume increased progressively, the greater increase occurring when the saline was equilibrated with 75% N_2O (Table I, Fig. 1). When the concentration of N_2O was the same in the inflating gas and the surrounding medium, balloon volume decreased. This decrease was greater with 75% N_2O than with 50% N_2O (Table I, Fig. 2). Inflation of the balloon with 100% CO_2 decreased volume on exposure to N_2O, the rate of decrease being greater with 50% N_2O than with 75% N_2O (Table I, Fig. 2). These decreases were greater when the balloon was filled with CO_2 than with N_2O at the ambient N_2O concentration (Table I, Fig. 2). Inflation of the balloon with CO_2 followed by exposure to air-equilibrated saline rapidly decreased balloon volume (Fig. 2).

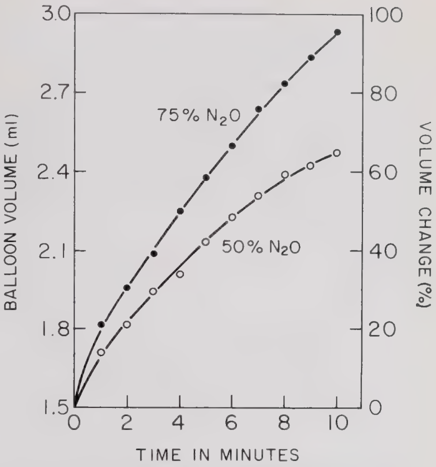

FIG. 1. Changes in balloon volume, with time, when the inflating gas is air (1.5 ml) and the surrounding medium is nitrous oxide in saline.

Inflation of the balloon with air, followed by exposure to saline equilibrated with 100% oxygen, increased balloon volume by 1% ± 3% at 5 minutes and 5% ± 13% at 10 minutes. Exposure of balloons inflated with air to saline equilibrated with air decreased volume by 1% ± 1% at 5 minutes and 2% ± 3% at 10 minutes.

The pressure required to inflate the balloons to 1.5 ml varied from 100 to 250 torr, indicating a wide range of compliance of the balloons. Three highly compliant balloons expanded very rapidly when exposed to 75% N_2O and ruptured (data not included).

Discussion

Our data confirm the finding by Kaplan et al that inflation of a Swan-Ganz catheter balloon

TABLE I

*Change in Balloon Volume**

Inflating gas	Units of change	Gas in surrounding saline					
		Air		50% N_2O		75% N_2O	
		5 min	10 min	5 min	10 min	5 min	10 min
Air	ml	−0.02 ± 0.02	−0.03 ± 0.05	0.64 ± 0.07	0.98 ± 0.04	0.88 ± 0.13	1.44 ± 0.19
	%	−1 ± 1	−2 ± 3	42 ± 5	65 ± 3	58 ± 9	96 ± 13
50% N_2O	ml	—	—	−0.14 ± 0.05	−0.27 ± 0.15	—	—
	%	—	—	−9 ± 3	−18 ± 10	—	—
75% N_2O	ml	—	—	—	—	−0.25 ± 0.05	−0.44 ± 0.12
	%	—	—	—	—	−17 ± 3	−29 ± 8
100% CO_2	ml	−0.97 ± 0.13	−1.12 ± 0.21	−0.47 ± 0.13	−0.74 ± 0.20	−0.31 ± 0.05	−0.57 ± 0.16
	%	−63 ± 9	−75 ± 14	−32 ± 9	−50 ± 13	−18 ± 3	−38 ± 11

* 1.5 ml inflating gas volume at zero minutes; saline at 37°C; values for five catheters are given as means ± SD.

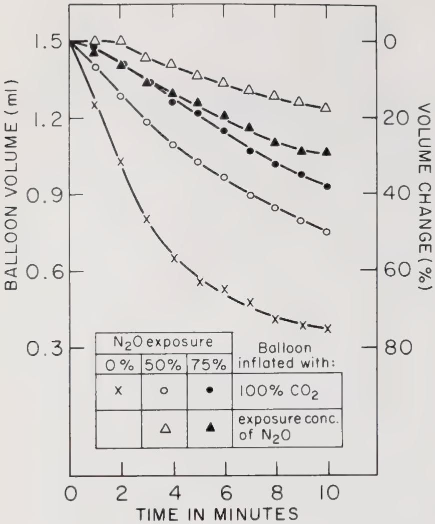

FIG. 2. Changes in balloon volume, with time, when the inflating gas is 1.5 ml of either 100% carbon dioxide (circles), or exposure concentration of N_2O (triangles), and the surrounding medium is nitrous oxide in saline or air in saline.

with air is followed by a further expansion of the balloon when the surrounding medium contains N_2O. Our results differ quantitatively, primarily in the rates at which the changes in volume occurred. Changes in our system were slower. Although Kaplan et al found that the maximum changes in volume occurred in 5 to 10 minutes, it is evident from both of our figures and from Table I that, at these times, the maximum changes have not been achieved. The delay in part may be accounted for by our use of the 1.5 ml volume recommended by the manufacturer. We observed that injection of 1.0 ml (as used by Kaplan et al) did not always result in balloon inflation. Our system also differed from that of Kaplan et al in our use of gas-equilibrated saline at 37°C rather than the gas itself as the medium surrounding the balloon. We have observed (unpublished data) that equilibration is affected by this difference in conditions. We chose saline because it more closely mimicked in vivo conditions. Regardless, both we and Kaplan et al have found large volume increases that occur within a time period pertinent to clinical practice.

We observed that a slow deflation of the balloon occurs when the concentrations of N_2O in the inflating gas and surrounding medium are similar. When the balloon was inflated with air and exposed to air and saline, volume decreased 2% over 10 minutes, while exposure to 100% oxygen resulted in an increase in balloon volume.

Edwards Laboratories recommends that filtered carbon dioxide be used for inflating the balloon of the Swan-Ganz catheter "because of its rapid absorption into the blood should the balloon rupture within the circulation". It states that CO_2 diffuses through the latex balloon, reducing its volume at a rate of approximately 0.5 ml/min. Our findings indicate that the rate is much less if the surrounding medium contains N_2O than if it contains air. The slower rate of decrease may provide greater safety if deflation of the balloon during passage into the pulmonary artery allows exposure of the catheter tip to traumatize the heart. It should be noted that if a slow deflation is desired, then inflation of the balloon with the gas delivered to the patient is probably as safe, and perhaps more safe, than inflation with CO_2 (Table I, Fig. 2).

The use of CO_2 or the delivered gas for balloon inflation may have one other desirable attribute. If the inflating gas becomes trapped in the balloon, it ultimately will escape by diffusing through the balloon wall. The rate of escape can be accelerated by changing the respired gases to 100% O_2. Inflation of the balloon with air renders this approach to balloon deflation impractical.

Considerable evidence indicates that flow-directed pulmonary artery catheters may induce morbidity and mortality (1–5). Excessive inflation may increase the difficulty of catheter insertion (6) or may cause damage to arterial walls by causing the catheter tip to deviate into the wall (7). Alternatively, the overinflated balloon itself may rupture the arterial wall (8). The various mechanisms whereby catheter-induced pulmonary artery perforation may occur have been discussed by Barash et al (9). Thus, for the patient anesthetized with nitrous oxide, it would appear desirable from all viewpoints to inflate the balloon with either the respired gas mixture or with 100% CO_2.

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Neurologic-Neurosurgical Notes

Allen E. Rubenstein, M.D. and Martin H. Savitz, M.D., Coeditors

Hypertrophic Synovitis of the Lumbar Facet Joint in Two Cases of Herniated Intervertebral Disc

MARTIN H. SAVITZ, M.D., S. SHELDON KATZ, M.D., HOWARD GOLDSTEIN, M.D., AND DOROTHEA WORCESTER, M.D.

Abstract

Two patients presented with signs and symptoms of a herniated nucleus pulposus. In both cases, myelography demonstrated an extradural filling defect at the right L4–5 level. During each of the operative procedures for laminotomy and diskectomy, a small pedunculated mass originating from the zygapophysial joint was excised. The etiology of this incidental synovial lesion is discussed.

Introduction

The histopathologic findings in synovial membranes following trauma are well known (1). Osteoarthritic changes in the facet joints are common in the presence of degenerative disc disease (2). Little mention has been made in the neurosurgical literature of hypertrophic synovitis of the zygapophysial joint presenting as a paraarticular mass.

Case Reports

Case 1: A 53-year-old woman suffered a low back injury by falling down a flight of stairs. Initially, her pain was localized to the lumbosacral area but, after several months, there was radiation into the right lower extremity. Following two separate trials of complete bed rest at home, she was admitted to the hospital. Neurologic examination demonstrated weakness of the right extensor hallucis longus, hypesthesia in the right L5 dermatome, and a depressed right ankle jerk. A myelogram (Fig. 1) confirmed a herniated intervertebral disc at the right L4–5 level.

The patient was taken to the operating room and underwent laminectomy. During the opening, as the muscle was separated from its attachments to the underlying spinous processes and laminae, a pedunculated tumor was uncovered with its stalk appearing just medial to the right L4–5 facet joint. The mass was approximately 1.5 cm in total length, 5 mm in its greatest diameter, and attached to a narrow pedicle. A biopsy was taken, and the bulk of the lesion was removed in pieces. As the facet was partially resected, the origin of the stalk was noted to be the zygapophysial joint. The diskectomy was then performed, and the findings were consistent with a herniated nucleus pulposus.

The microscopic sections of the pedunculated mass revealed fibroconnective tissue with areas of old hemorrhage, articular cartilage, and synovial membranes (Figs. 2–4). There were no neoplastic cells. The histologic features were diagnostic of hypertropic synovitis.

Postoperatively, the patient became free of pain. The strength in her right extensor hallucis longus returned to normal. During a two year follow up, there has been no recurrence of lumbar radiculitis.

Case 2: A 71-year-old woman with a long his-

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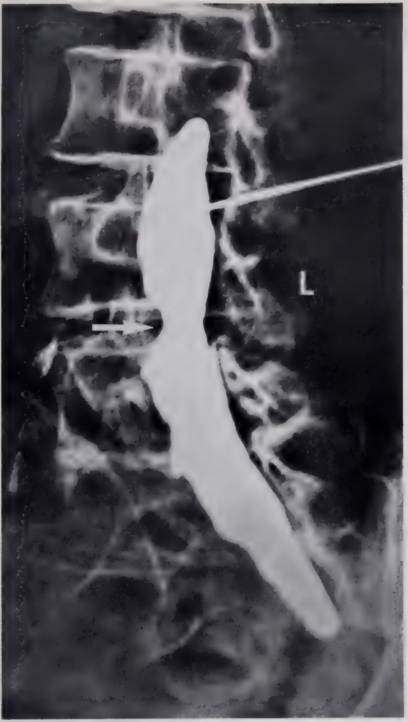

FIG. 1. Lumbar myelogram, left anterior oblique projection. Note lateral indentation on the opaque column at the right L4–5 level (arrow).

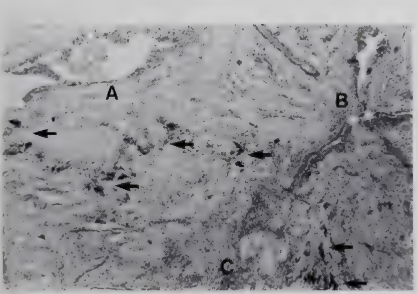

FIG. 2. Medium-power view of lesion characterized by large synovial cleft (A), other slit-like clefts (B), articular cartilage (C), and multiple areas of hemosederin-laden phagocytes (arrows) in the stroma.

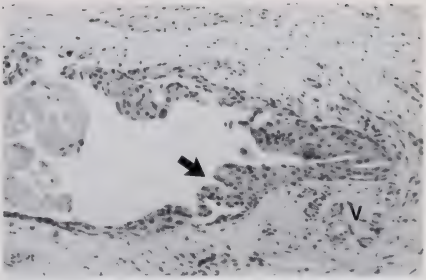

FIG. 3. High-power view of synovial cleft showing invaginations bordered by enlarged hystiocytes (arrow). Note matrix consisting of elongated cells with small blood vessels (V) forming a variable pattern and lacking any malignant changes.

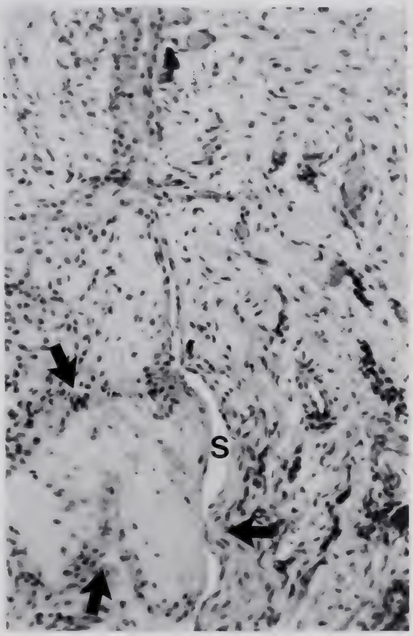

FIG. 4. High-power view of articular cartilage embedded in connective tissue (arrows) and bordering slit-like synovial sinus (S).

tory of arthritic pains in multiple joints developed right sciatica. She was hospitalized after an eight-week course of physiotherapy failed to provide relief of her symptoms. Approximately two years prior to her admission, she suffered a right

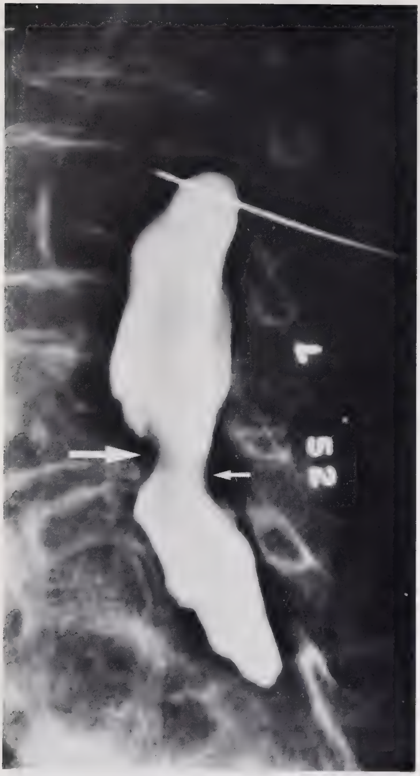

FIG. 5. Lumbar myelogram; left anterior oblique projection. Note indentation of the opaque column on the right lateral aspect at the L4–5 level (large arrow). There is an associated prominent posterior filling defect (small arrow) due to hypertrophy of the ligamentum flavum.

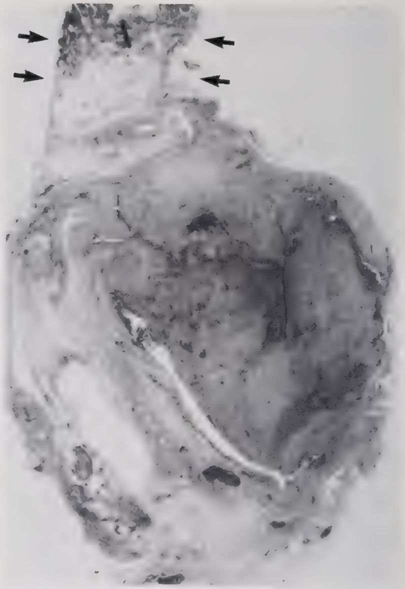

FIG. 6. Low-power cross sectional view of entire encapsulated lesion, showing many villous clefts interweaving in multinodular stroma with areas of hemosederin. Note connective tissue stalk (arrows).

cerebrovascular accident with residual left-sided weakness. Neurologic examination revealed left facial weakness, left hemiparesis, left hyperreflexia, hypesthesia in the right L5 and S1 dermatomes, and an equivocal left Babinski sign. A myelogram (Fig. 5) showed a herniated intervertebral disc at the right L4–5 level.

The patient was taken to the operating room and underwent laminectomy. During the opening, a similiar encapsulated mass was found arising from the dorsal capsule of the right L4–5 zygapophysial joint. The entire pedunculated lesion was amputated from the joint capsule prior to entering the disc space. The microscopic findings were again consistent with hypertrophic synovitis (Fig. 6). Postoperatively, her right sciatica resolved; but the patient continued to be symptomatic with episodic low back pain.

Discussion

Degenerative changes in the intervertebral disc are generally associated with severe damage to the posterior joints. The most minor strains of the lumbar articular ligaments produce synovitis of the facet joint. When the synovium is torn, hemarthrosis results. As in all diarthrodial joints, fibrillation and degeneration of cartilage occurs with erosion. Osteophytosis forms at the periphery, or the entire articular process may increase in size (3).

Changes in the joint capsule accompany changes in the articular surfaces. The dorsal capsule thickens and frequently develops areas of cartilage within its substance. In studies of autopsy specimens, nodules considered primarily cartilaginous in origin have been described as varying in size from barely visable to large masses protruding like beads behind and below the facet articulations (4).

In our own two cases, the articular cartilaginous ligaments became lax and redundant. With continuing avulsion, reinjury, and scarring, synovial loculations were formed. Caught inside were fibrotic elements, connective tissue, and clefts representing synovium that had collapsed. The authors believe these paraarticular masses to be extreme examples of a common pathologic process.

Acknowledgment

The authors wish to express their thanks to Dr. Austin D. Johnston for reviewing the histologic sections.

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Neurologic-Neurosurgical Note

Allen E. Rubenstein, M.D. and Martin H. Savitz, M.D., Coeditors

Sudden Onset of Involuntary Movement Disorders with Arteriovenous Malformations of the Basal Ganglia

MARK S. DIAMOND, M.D., YUN PENG HUANG, M.D., AND MELVIN D. YAHR, M.D.

Abstract

Two cases of sudden onset of involuntary movement disorders due to cerebral arteriovenous malformations are reported. Diagnosis was established by computed tomography and angiography. The clinical and radiologic characteristics of the lesions are discussed.

Introduction

Discrete structural lesions of the brain as a cause of extrapyramidal dysfunction are uncommon. Cerebral arteriovenous malformations (AVM's), causing extrapyramidal symptoms and signs are rare (1). We report two cases of AVM's of the basal ganglia associated with sudden onset of involuntary movement disorders. The radiographic features of these lesions and a review of the literature are presented.

Case Reports

Case 1: A thirty-nine-year old hispanic male was in his usual state of good health until an automobile accident two and one half months prior to admission. He lost consciousness but was released from a hospital emergency room. One to two weeks after the accident he noticed violent inconstant shaking of his left arm which varied with body and arm position. It disappeared when he was supine. He also complained of pain in the occiput and neck. In addition, he noticed a noise in his right ear which was not previously present. He denied seizures, visual-disturbances or episodes of loss of consciousness. There was no family history of neurologic disease and the patient was not taking drugs.

On admission, the general physical examination was normal. No bruits could be heard over the head or eyes. Mental status was normal. Minimal left facial weakness was present. Motor strength and tone were normal. The sensory examination was normal. Deep tendon reflexes were symmetric and no Babinski sign could be elicited. A very coarse large amplitude tremor of the left arm occurred when performing the finger-to-nose test. This was greater proximally than distally. At times it disappeared completely when the patient was supine and when the left arm was fully extended. It was not present at rest. Rapid alternating movements were impaired in both the left hand and left foot. Heel-knee-shin testing was slightly impaired on the left. Gait and station were normal.

Cerebrospinal fluid studies were normal as was the electroencephalogram. A computed tomographic (CT) brain scan performed with contrast material revealed ill-defined streaky enhancement within the right anterior temporal lobe and diffuse enhancement of the right basal ganglia consistent with an AVM. A large basal vein of Rosenthal was noted. There was displacement of the mid and upper brain stem from right to left secondary to aneurysmal dilatation of the basal

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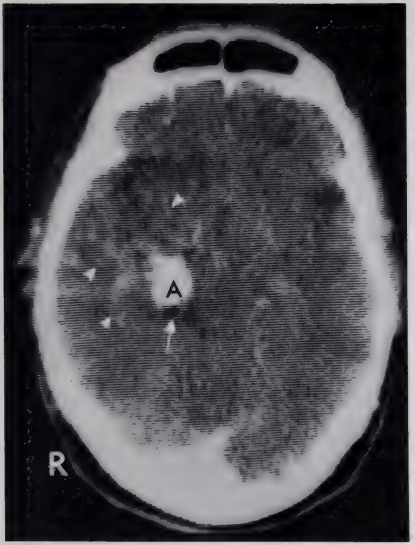

FIG. 1. CT scan of the head demonstrating an AVM involving the temporal lobe and basal ganglia on the right side with a large aneurysmal dilatation of the ipsilateral basal cerebral vein.

FIG. 1A. CT section through the upper brain stem. Streaky, mottled enhancements representing medullary veins are seen in the mid and anterior portions of the right temporal lobe (arrowheads). A large venous aneurysmal dilatation (A) receiving these medullary veins is seen displacing the brain stem, causing widening of the circumesencephalic cistern (arrow). The right side (R) of the head is labeled.

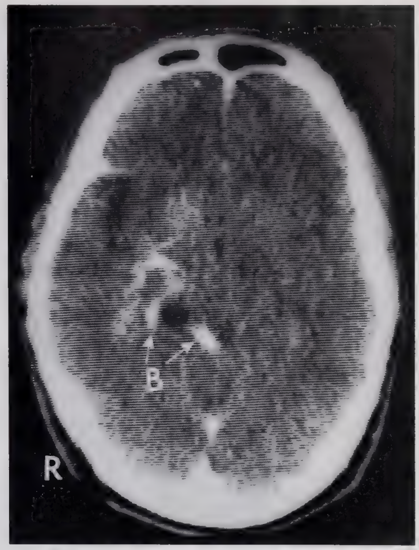

FIG. 1B. Section 8 mm above the level shown in Fig. 1A. The medullary veins seen as enhanced streaks in the medial temporal lobe, draining mainly into the basal cerebral vein of Rosenthal (B), partly seen, can be identified.

cerebral vein within the circum-mesen cephalic cistern on the right (Fig. 1A, 1B, 1C). Cerebral angiography was performed and further delineated a large AVM involving the temporal lobe and basal ganglia on the right (Fig. 2A & 2B).

During his hospital stay, the patient became acutely agitated with paranoid and suicidal ideation and was transferred to the psychiatry service. He was treated with haloperidol which rapidly improved his psychiatric problems. The left arm movements remained unchanged. One episode of focal motor seizures of the left face occurred and the patient was treated with diphenyl hydantoin. He was discharged in good condition but with his left arm tremor unchanged. He remains clinically unchanged eight months after his initial symptoms.

Case 2: A sixty-seven-year-old white female was seen at The Mount Sinai Hospital. At age fifty-eight, she noted the sudden onset of wild jumping movements of the left arm. She was seen at a number of medical centers and a trial of

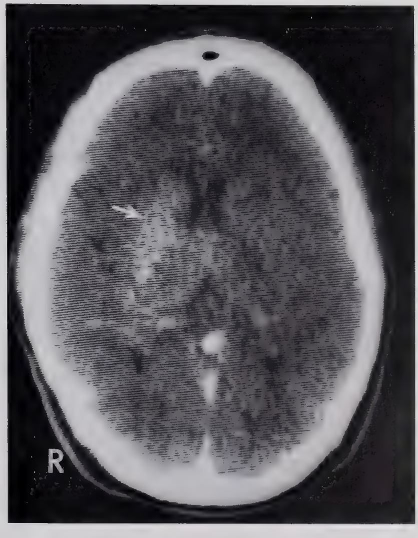

FIG. 1C. Section 8 mm above the level shown in Fig. 1B. Mottled enhancement is noted in the basal ganglia and, to a lesser extent, with the thalamus on the right.

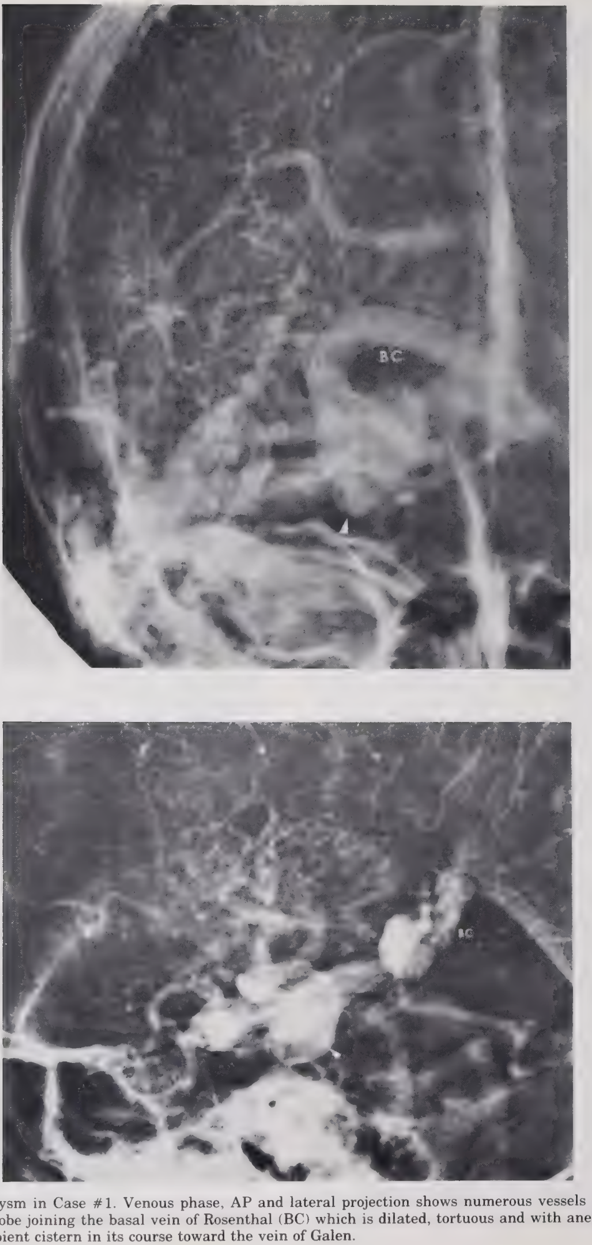

FIG. 2A & B. Aneurysm in Case #1. Venous phase, AP and lateral projection shows numerous vessels draining the basal ganglia and temporal lobe joining the basal vein of Rosenthal (BC) which is dilated, tortuous and with aneurysmal dilatation (arrowhead) in the ambient cistern in its course toward the vein of Galen.

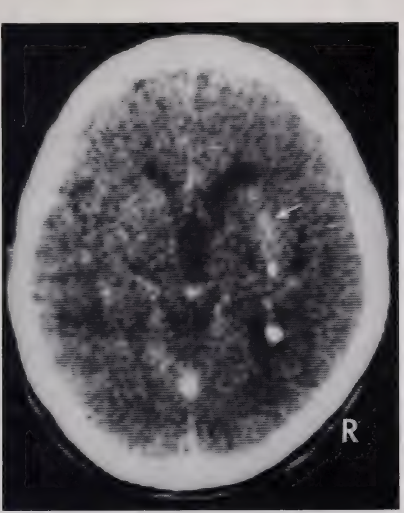

FIG. 3. CT scan of the head through the basal ganglia in the inferior orbitomeata plane. The basal ganglia is enhanced (arrow). A small enhanced dot represents a large parenchymal draining vein within the posterior part of the thalamus, most likely representing arteriovenous malformation.

haloperidol was instituted without benefit. The movements gradually improved over the years. At age sixty-seven she began to feel that her left leg was "floppy." Her past medical history was significant for Sydenham's chorea as a child.

The general physical examination was normal. Choreoathetoid movements of the left hand and left leg were prominent; the hand was more involved than the leg. The remainder of the neurologic examination was normal.

A CT brain scan was performed. This revealed an abnormal area of enhancement involving the right basal ganglia region (Fig. 3) which was interpreted as indicative of an AVM. There was no mass effect. The ventricles and sulci were slightly widened. The patient refused cerebral angiography.

Discussion

Despite the plethora of vascular supply to the basal ganglia area AVM's in this region are not common. In one series of 110 cases of intracranial AVM's, only nine were in the basal ganglia region (2). In the series of 105 cases from the Lahey Clinic, only six were in the basal ganglia area (3). A previous survey quotes a figure of 7.6% of supratentorial AVM's in the basal ganglia (1).

The most common manifestations of intracranial AVM's are hemorrhage, convulsive seizures and headache. Extrapyramidal dysfunction is rare. In the series reported by Paterson and McKissock, one patient with a "central" AVM is described with athetoid-type movements of the hemiparetic limbs (2). Shaw et al reported one case of chronic spasmodic left torticollis presenting two years after subarachnoid hemorrhage, due to AVM although the location of the AVM was not well described (4). The series reported by Lobo-Antunes et al describes four cases (1). Two had tremor and dystonia, one had torticollis, and one had retrocollis. Of the AVM's in that series, three were in the thalamic and basal ganglia region and one in the right parietal lobe. Podlas et al reported one case with a thalamic AVM and contralateral "tremor" and "extrapyramidal signs" (5).

The possible pathophysiologic mechanisms involved have been previously presented (1). These are: 1) shunting of blood through an AVM with resultant "steal effect" from normal structures, 2) mass effect upon the basal ganglia by the AVM itself or by hematomas formed as a result of hemorrhage and 3) abnormalities of brain tissue development associated with the abnormal blood vessel development. This third postulated mechanism would not be applicable in late onset cases such as ours. Of particular interest in the two cases presented here is the suddenness of onset of the movement disorder reported by the patients. It is conceivable that this resulted from sudden breakdown or hemorrhage within the AVM leading to damage to the adjacent structures via either mass effect or "steal effect" as described above. However, Weisberg performed CT scans in 12 patients 48 to 96 hours after an acute, nonepileptic presentation of proven AVM's (6). In four of these 12, there was no CT scan evidence of either mass effect, infarction or hemorrhage.

Also of interest is the amelioration of symptoms seen in case 1 when the patient was recumbent. This was so striking as to convince some observers that the patient was hysterical. We can provide no satisfactory explanation of this phenomenon although perhaps it could be related to altered hemodynamics within the AVM.

The current treatment alternatives for cerebral AVM's have recently been reviewed (7, 8). Any management decision regarding these lesions should take into account the natural history of the disease, the risk inherent in any method of intervention, and the status of the patient. Svien and McRae reported on the long term follow-up of 68 patients with documented cerebral AVM's managed conservatively (9). They found a mortality rate of 16%. Of the survivors, 10% were invalids, and 22% were self-supporting despite symptoms. Fully 68% were leading normal lives. A recent study of 50 patients treated conservatively cites a mortality rate of 20% (10). 36% of these patients deteriorated neurologically while 10% improved. 42% remained unchanged.

Despite the significant risks of conversative management, deeply-seated lesions such as in the two patients presented here have historically been considered inoperable. With advances in microsurgical technique, stereoangiography, and selective arterial embolization, there have been a number of recent reports successful removal and/or obliteration of these lesions (5, 11−13). However, intervention must still be considered only in selected cases where interruption of the major feeding vessels will not compromise the nearby vital structures. The importance of gradual rather than sudden dynamic circulatory changes within and around the AVM in determining the successful outcome of any intervention has recently been emphasized (7, 8). As further advances in understanding and technique occur, AVM's in the basal ganglia region may become more amenable to surgical and/or embolic treatment.

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Gaucher Disease (1882–1982): Centennial Perspectives on the Most Prevalent Jewish Genetic Disease

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Abstract

On the one hundredth anniversary of Gaucher's original description, the major advances in the delineation and understanding of this inherited metabolic disease are reviewed. In particular, the contributions of the early Mount Sinai investigators are highlighted. Current research efforts are directed to elucidate the molecular genetic pathology and to develop efficacious therapy. The major obstacles to these goals are discussed.

Introduction

One hundred years ago, Philippe Charles Ernest Gaucher (Fig. 1) described the first case of Type 1 Gaucher disease in a 32-year-old woman who had remarkable splenomegaly (1). These clinical and pathologic studies were part of this 28-year-old physician's medical thesis, entitled "De L'epithelioma Primitif De La Rate, Hypertrophie Idiopathique De La Rate Sans Leucemie" (Fig. 2). From his microscopic examination of postmortem material, he suggested that the peculiar, large cells in the massively enlarged spleen (now called "Gaucher cells") were the result of a primary splenic neoplasm. Although this disease was later recognized to be a systemic metabolic disorder, his initial report stimulated interest in the medical communities of Europe and North America. By 1901, several additional cases had been identified, and the eponym, "Gaucher disease" had been introduced into the medical literature by Mount Sinai pathologist, Nathan E. Brill (2). Although Gaucher did not continue to work on this disease, the eponym has been retained in recognition of his original contributions. Gaucher remained in academic medicine, published work on the cutaneous manifestations of syphilis and on renal disease, and in 1902 became the Professor of Dermatology at the University of Paris.

It is appropriate on the one hundredth anniversary of Gaucher's original description to review the historical highlights in the delineation of this disease. Many of these important contributions were made by physicians at The Mount Sinai Hospital. In addition to the advances in the delineation and understanding of this disease, the problems remaining to be solved are also discussed in this centennial perspective on Gaucher disease, the most prevalent Jewish genetic disease.

Clinical And Pathologic Delineation

During the past century, physicians and scientists have made important contributions to the delineation and understanding of this disease (Table I). Shortly after Gaucher's original description, additional cases were discovered in both Europe and the United States (2–5). These investigators observed the primary splenic pathology and noted the associated involvement of the lymph nodes (3, 4), liver (5), and bone marrow (6). The systemic nature of the disease was first recognized by Schlagenhaufer in 1907 (7). He suggested that the disease was "a systemic disor-

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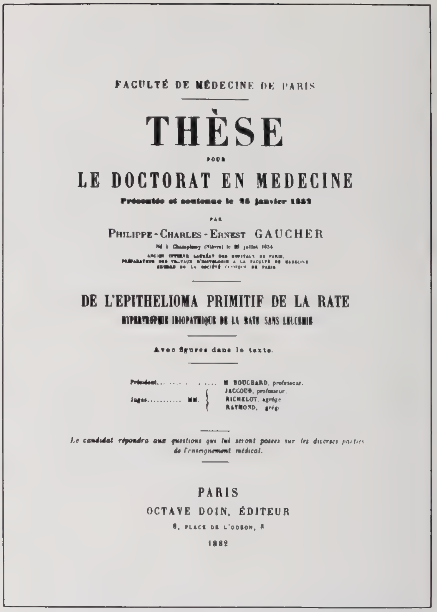
FIG. 1. Philippe Charles Ernest Gaucher, M.D. (1854–1918)



FACULTÉ DE MÉDECINE DE PARIS

THÈSE

POUR

LE DOCTORAT EN MEDECINE

Présentée et soutenue le 28 janvier 1882

PAR

PHILIPPE-CHARLES-ERNEST GAUCHER

Né à Champlemy (Nièvre) le 26 juillet 1854

ANCIEN INTERNE, LAURÉAT DES HOPITAUX DE PARIS,
PRÉPARATEUR DES TRAVAUX D'HISTOLOGIE A LA FACULTÉ DE MEDECINE
MEMBRE DE LA SOCIÉTÉ CLINIQUE DE PARIS

DE L'EPITHELIOMA PRIMITIF DE LA RATE

HYPERTROPHIE IDIOPATHIQUE DE LA RATE SANS LEUCEMIE

Avec figures dans le texte.

Président.............. M. BOUCHARD, professeur.
Juges........... MM. JACCOUD, professeur.
RICHELOT, agrégé
RAYMOND, agrég

Le candidat répondra aux questions qui lui seront posées sur les diverses parties de l'enseignement médical.

PARIS
OCTAVE DOIN, ÉDITEUR
8, PLACE DE L'ODÉON, 8
1882

FIG. 2. Title page of Dr. Gaucher's medical thesis.

der of the lymphatic-hematopoietic apparatus, with proliferation of the reticular structures." Other etiologies for the pathologic findings were advanced; these included neoplastic processes, chronic infection, endothelial proliferation, or the irritating effect of an unknown toxin (5). Marchand, in 1907 (8), was the first to suggest that the pathologic cellular involvement was due to the storage of a semisolid hyaline-like material; however, his insight was not fully appreciated until years later.

Notable among the early clinical and pathologic descriptions of the disease were those of three physicians at The Mount Sinai Hospital in New York City: Drs. Nathan E. Brill, Fredrick S. Mandelbaum and Emanuel Libman (Table II). In 1901, Dr. Brill (Fig. 3) was the first to suggest that the disease was a familial disorder (2). Three years later, he reported the occurrence of Gaucher cells in the bone marrow and, based on these findings, was the first to diagnose a case during life (6, 9). During the next ten years, Drs. Mandelbaum (Fig. 4), Libman (Fig. 5) and Brill extensively described the anatomic and morphologic pathology of this disease. They recognized that the unique clinical and pathologic features were distinct from those of other disorders characterized by splenomegaly, and were the first to designate this disorder as "Gaucher's disease."

Although Collier described the disease in a 6-year-old child in 1895, the first cases of Gaucher disease in infants were reported by Kraus in 1920 (10) and Rusca in 1921 (11). The severe neurologic involvement of the infantile onset disease was emphasized in 1927 by Oberling and Woringer who recognized that the infantile neuronopathic (Type 2) and the later onset (Type 1) diseases were related, but distinctly different entities (12). About thirty years later, Hillborg (13) described the first cases of Gaucher disease in Sweden. These patients were from small, inbred communities in the Norrbottnian area, near the Arctic Circle. The "Norrbottnian" type was unique, with clinical onset during childhood, characterized by hepatosplenomegaly and subsequent neurologic involvement. This form (Type 3) has been designated juvenile or subacute neuronopathic Gaucher disease.

The distinguishing features of the three types of Gaucher disease are compared in Table III. The differentiation of young children with Type 1 (nonneuronopathic) disease and infants with the

TABLE I
Gaucher Disease: A Century of Delineation and Understanding

Year	Discovery	Investigator
Clinical and Pathologic Delineation		
1882	Type 1 Disease; "Gaucher Cells"	Gaucher
1895–1896	Lymph Node Involvement	Collier; Picou & Raymond
1904	Bone Marrow Infiltration	Brill
1904–1913	Morphologic Pathology	Brill et al; Risel
1907	Systemic Disorder	Schlagenhaufer
1920–1921	Type 2 Disease	Kraus; Rusca
1959	Type 3 Disease ("Norrbottnian Type")	Hillborg
Metabolic Defect		
1907	"Hyaline Substance" Stored in Cells	Marchand
1916	Metabolic Lipid Disturbance	Mandelbaum & Downey
1924	*Galacto*cerebrosidosis (Kerasin)	Lieb; Epstein
1934	*Gluco*cerebroside Accumulation	Aghion
1956	Elevated Serum Acid Phosphatase	Tuchman et al
1965	Defective Glucocerebrosidase	Brady et al; Patrick
1968	Defective β-Glucosidase	Ockerman
1968	Lysosomal Localization	Weinreb et al
1971	Effector Molecule	Ho & O'Brien
Genetics		
1901	Familial Disorder	Brill
1948	Autosomal Dominant Inheritance	Groen
1950	Autosomal Recessive Inheritance	Herndon & Bender
1958	Ashkenazi Jewish Predilection	Fried
1981	Gene Assignment	Devine et al
Diagnosis & Management		
1970	Heterozygote Detection	Beutler & Kuhl
1972	Prenatal Diagnosis	Schneider et al
1974	Enzyme Replacement Trials	Brady et al

severe neurodegenerative course of Type 2 disease was recognized in the 1920's (12, 14). Subsequently, Aballi and Kato (15) reviewed all the cases reported in infancy, delineated the clinical features of Type 2 disease, and further distinguished this subtype from patients with an early onset of Type 1 disease manifestations. With the report of more cases, the variable age of onset in patients with Type 1 disease was recognized. For example, splenomegaly was observed in Type 1 patients during the first year of life (14, 15). Of particular note were the asymptomatic individuals with Type 1 disease who were diagnosed serendipitously in their seventh, eighth or ninth decade of life while being evaluated for unrelated medical problems. The oldest patient reported was an asymptomatic eighty-six-year old Jewish man, who was admitted to The Mount Sinai Hospital in 1960 with jaundice due to chlorpropamide induced hepatocanalicular injury; the presence of anemia and thrombocytopenia prompted a bone marrow examination which revealed the diagnosis (16). It was notable that this patient did not have splenomegaly. Such cases provided documentation of the extreme variation in the clinical expressivity of the Type 1 disease, that is, from early onset with severe visceral involvement and demise in childhood to totally asymptomatic individuals diagnosed by chance in late maturity. In the early literature, and even to some extent today, a diagnosis in early childhood has led to confusion in the classification of the disease sub-

TABLE II
Contributions by the Early Mount Sinai Investigators of Gaucher Disease

Year	Mount Sinai Investigator	Contribution
1901	Nathan E. Brill	Familial Disorder
1904–1919	Nathan E. Brill Fredrick S. Mandelbaum Emanuel Libman	Clinical Delineation; Histologic & Histochemical Pathology
1956	Lester R. Tuchman	Elevated Serum Acid Phosphatase Activity

FIG. 3. Nathan E. Brill, M.D. (1860–1925)

FIG. 4. Fredrick S. Mandelbaum, M.D. (1867–1926)

type, particularly in non-Ashkenazi Jewish individuals. Moreover, the arbitrary designation of "infantile," "juvenile" or "adult" subtypes has resulted in misclassification of nonneuronopathic cases and incorrect information/counseling concerning prognosis. The underlying pathophysiology of the remarkable clinical variation, especially that observed among Ashkenazi Type 1 patients, remains unexplained.

Metabolic Defect

The first studies of the molecular pathology in Gaucher disease were based on the 1907 studies of Marchand (8) who observed a hyaline like storage material in reticuloendothelial cells. The Mount Sinai group pursued the chemical etiology of the disease in collaboration with Dr. Hal Downey of the University of Minnesota. In 1916, Drs. Mandelbaum and Downey performed the first histochemical studies on frozen and formalin-fixed sections of Gaucher spleen. Based on their observations, they concluded that

> the peculiar substance in the cells which is so characteristic of Gaucher's disease and which has never reacted definitely to any micro-chemical methods for lipoids, is not of a pure lipoid nature. Our analyses show that this substance does not lie in the extractive group and hence must be of complex protein nature, possibly in combination with phosphatids, which seem to be increased in our cases. (17)

They were among the first to implicate a metabolic defect as the cause of Gaucher disease. Subsequently, in 1924 Lieb (18) and Epstein (19), in association with Lorenz (20), demonstrated that the accumulated material was galactocerebroside or kerasin. Epstein isolated a substance from Gaucher spleen which was soluble in alcohol and insoluble in acetone. Lieb identified the stored material as kerasin, a major lipid component of brain. It was not until 1934 that Aghion in Paris demonstrated that the accumulated cerebroside in the spleen from a Type 1 patient contained glucose and not galactose, and thereby accurately identified the stored material as glucocerebroside or glucosyl ceramide (21). His findings were confirmed by Halliday et al in 1940 (22) and subsequently by Klenk (23), Danielson et al (24), and others as reviewed by Schettler and Kahlke (25). Thannhauser and coworkers documented the accumulation of glucocerebroside in the spleen from a Type 2 patient (26). Only recently, Svennerholm and colleagues demonstrated the accumulation of the related compound, glucosyl psychosine, in tissues from patients with Type 3 disease (27).

FIG. 5. Emanuel Libman, M.D. (1872–1946)

Following the identification of the stored material, investigators began to consider Gaucher disease a disorder of intracellular metabolism, due to a disturbance of the enzymes involved in the synthesis or degradation of sphingomyelin and cerebrosides (28). In 1933, Pick (29) suggested that a general abnormality in intermediary lipid metabolism was expressed by an accumulation of cerebrosides in the serum which were secondarily stored in reticular cells. In contrast, Thannhauser in 1953 (30) believed that a

> dysfunction of the reticular cells themselves, as a result of an enzymatic disturbance within the cell, . . . [lead] to an increased synthesis of cerebrosides, and simultaneously to a storage of these substances within the cell.

The latter concept was generally accepted until the specific metabolic defect was identified.

In 1956, another significant contribution was made by Mount Sinai investigators. Lester R. Tuchman (Fig. 6) and his colleagues reported the first enzyme abnormality in Gaucher disease, the elevated activity of serum acid phosphatase (31). The increased level of nontartrate inhibitable serum acid phosphatase provided an easily performed biochemical marker that was useful for the diagnosis of patients with Gaucher disease (32). In 1960, Trams and Brady (33) demonstrated that the synthesis of glucosyl ceramide in Gaucher spleen occurred at a normal rate, thus abrogating Thannhauser's (28, 30) hypothesis that increased cerebroside synthesis was the cause of the disease. Subsequently in 1965, Brady and colleagues (34) in the United States and Patrick (35) in England, definitively demonstrated that the primary metabolic defect was the deficient activity of the enzyme, glucocerebrosidase (Fig. 7). This was the first enzymatic defect identified among the sphingolipidoses. This enzyme was also identified and characterized from mammalian sources by Gatt and Rapport (36), and the human enzyme was shown to be an acid β-glucosidase by Ockerman (37). Weinreb and coworkers (38) demonstrated its lysosomal localization, thus classifying Gaucher disease among the lysosomal storage disorders. In 1971, Ho and O'Brien (39) described a low molecular weight glycoprotein "effector molecule" which binds the enzyme, but whose physiologic role in substrate metabolism remains unclear. The terminology used for the enzyme and substrates in Gaucher disease is shown in Table IV.

Genetics

Although Collier (3) and Bovaird (5) each described sisters affected with Type 1 disease in two

TABLE III

Gaucher Disease—Clinical Subtypes

Clinical Features	Type 1 Nonneuronopathic	Type 2 Acute Neuronopathic	Type 3 Subacute Neuronopathic
Clinical Onset	Childhood/Adulthood	Infancy	Childhood
Hepatosplenomegaly	+	+	+
Hematologic Complications Secondary to Hypersplenism	+	+	+
Skeletal Deterioration	+	−	+
Neurodegenerative Course	−	+++	++
Death	Variable	By 2 yr	2nd-4th Decade
Ethnic Predilection	Ashkenazi Jewish	Panethnic	Swedish

FIG. 6. Lester R. Tuchman, M.D. (1901–)

unrelated families, neither commented on the familial nature of the disease. In fact, Bovaird stated that "the occurrence of two cases in sisters in the report of Collier and the same phenomena in the writer's cases is worthy of note. This feature of the cases certainly suggests the action of some system poison affected several members of a family." In contrast, Brill (2) reported three affected siblings in 1901 and was the first to ascribe a familial nature to the disorder, at the same time that Mendelism was being rediscovered. Later, he diagnosed a fourth case among the six siblings in this family (2, 6). After reviewing the literature, he concluded:

> I can furnish no further explanation of this affection, and all that can be said about this special class of cases is that they represent probably a family disease whose essential characteristic is a progressive splenomegaly. When the physiology and pathology of the spleen become known, it may be possible to refer this class of cases to its proper place in medical nosology.

Even though the familial nature of Type 1 disease was appreciated in early reports, Bloem, Groen and Postma in 1936 were the earliest investigators to actually suggest, rather than imply, genetic transmission (40). Groen, in 1948, formally investigated the inheritance of the disease (41). He reviewed the information on 89 cases in 31 families. In two of these families, the disease was observed in two generations. He concluded that "the mechanism of transmission in Gaucher's disease appears to be following the genetic rules for one single dominant trait." It was not until 1950 that Herndon and Bender reported five closely related Black families with Type 1 disease (42). Since the parents of four of the affected individuals were second cousins, and since consanguineous matings bring rare recessive genes into the homozygous state, they concluded that Gaucher disease was due to an autosomal recessive gene. They further postulated that the defective gene in the homozygous condition resulted in an intracellular defect in cerebroside metabolism. Subsequently, Hsia et al in 1959 reassessed the mode of inheritance after evaluating 110 informative families from the literature (43). Having separated families with Types 1 and 2 disease, they concluded that each subtype was inherited as an autosomal recessive trait either due to separate alleles at one locus or

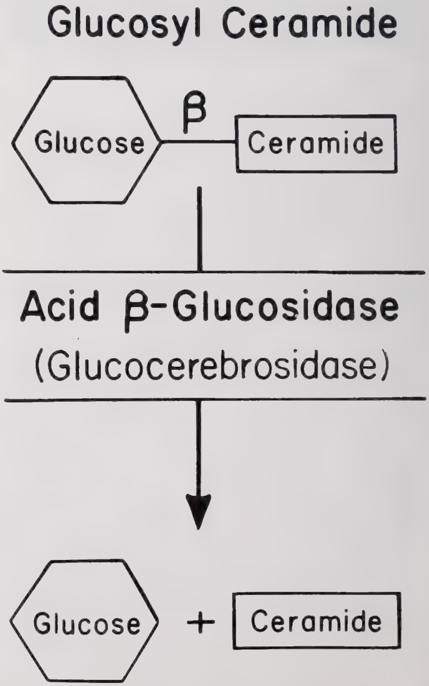


FIG. 7. The metabolic defect in Gaucher disease.

TABLE IV

Synonyms for the Defective Enzyme and Its Natural Substrates

Enzyme	Substrates
ACID β-GLUCOSIDASE*	GLUCOSYL CERAMIDE
β-Glucosidase	Glucocerebroside
Glucocerebrosidase	N-Acylsphingosine-β-D-Glucoside
Glucosylceramidase	
Cerebroside-β-Glucosidase	
Glucocerebroside-β-Glucosidase	GLUCOSYL PSYCHOSINE
Glucosylceramide:β-Glucosidase	Glucopsychosine
D-Glucosyl-N-Acylsphingosine-Glucohydrolase (EC 3.2.1.45)	Sphingosyl-β-D-Glucoside

* Preferred nomenclature capitalized

two separate loci (44). In addition, their analyses contradicted the two suggestions by Groen (45) that 1) there was an increased frequency of miscarriages and neonatal deaths among the offspring of patients with Type 1 disease, and 2) the disease became increasingly severe in successive generations (44).

Although Reich et al in 1951 noted that 95% of the reported cases were Jewish (46), the prevalence of the disease among Ashkenazi Jews was first emphasized by Fried in 1958 (47). Subsequently, Fried and colleagues estimated the incidence of Type 1 Gaucher disease among Ashkenazi Jews in Israel at 1:2,500; the gene frequency was estimated at 0.02 (47, 48). Although Tay-Sachs and Gaucher diseases have the same estimated incidence in the Ashkenazi population, Tay-Sachs disease is lethal early in childhood, whereas most patients with Type 1 Gaucher disease survive. Thus, Type 1 Gaucher disease is the most prevalent of the Jewish genetic diseases among Ashkenazim (Table V). For example, it is estimated that in the greater New York metropolitan area alone, there are from 1,000 to 1,500 affected individuals with Type 1 disease, and from 120,000 to 160,000 Jewish individuals who are carriers of the disease-causing gene.

Recently, efforts have been directed to localize the gene for Gaucher disease to a specific human chromosome. Using somatic cell hybridization techniques, the chromosomal location of the structural gene for acid β-glucosidase has been identified on the long arm of human chromosome 1 by Shafit-Zagardo et al (49). Finer localization has been made to a small segment at the end of the long arm (1q42 → 1qter) as reported by Devine et al (50).

Diagnosis and Management

Following the identification of the specific enzymatic defect in patients with Type 1 disease (34), deficient acid β-glucosidase activity was also documented in patients with Type 2 (51) and Type 3 disease (52). These findings provided the basis for the precise enzymatic diagnosis of affected individuals with all three subtypes, even before the onset of clinical manifestations. In addition, determination of the acid β-glucosidase activity using commercially available, artificial substrates permitted the development of methods for

TABLE V

Inherited Diseases Among Ashkenazi Jews

Disease	% Jewish	Incidence Estimates*	
		Jewish	General
Gaucher Disease, Type 1	99	1:2,500 (Israel)	rare
Tay-Sachs Disease	99	1:2,500 (USA)	1:360,000
Essential Pentosuria	99	1:2,500 (USA) 1:5,000 (Israel)	very rare
Familial Dysautonomia (Riley-Day Syndrome)	99	1:10,000 (USA) 1:12,500 (Israel)	very rare
PTA (Factor XI) Deficiency	90	1:12,000 (USA)	very rare
Spongy Brain Degeneration	85	?	?
Dystonia Musculorum Deformans	80	1:17,000 (USA)	?
Abetalipoproteinemia	66	1:20,000	?
Bloom's Syndrome	60	1:160,000 (Israel)	very rare
Niemann-Pick, Type A	50	1:25,000	very rare

* After Goodman (82)

identification of carriers (53) and for the prenatal diagnosis of affected fetuses with all three subtypes (54–56). It should be noted that carrier detection methods require either the isolation of peripheral leukocytes or the establishment of cultured skin fibroblast lines from individuals to be tested. Carrier identification using cultured fibroblasts has proven reliable; however, the time, effort, and expense required to establish these cultures prohibits their use for mass screening. To date, leukocytes have not proven to be a reliable source for carrier detection due to the significant overlap in the values obtained for normal individuals and known carriers of the Gaucher Type 1 gene. Thus, newer, more precise methods for carrier detection must be developed prior to the initiation of mass screening programs for Gaucher carriers in the Ashkenazi Jewish population analogous to those for Tay-Sachs disease.

During the past several years, efforts have been directed toward the evaluation of enzyme replacement therapy for this disease (57–59). Although biochemical changes have been observed following the intravenous administration of the normal enzyme to patients with Type 1 or 3 disease, clinical improvement has not been documented. The therapeutic effectiveness of this approach awaits further refinement of enzyme targeting techniques and long-term evaluation. In the absence of specific treatment, clinical management of disease manifestations and complications remains supportive. Such management includes the careful monitoring of hematologic and orthopedic problems. Decisions regarding appropriate medical intervention, particularly with regard to splenectomy and orthopedic procedures, should be made by physicians expert in the various complications of this disease.

Problems To Be Resolved

Clearly, the past century has witnessed the delineation of the clinical, pathologic, biochemical and genetic aspects of this disease. Increased understanding of the disease process and its molecular pathology has provided the basis for better patient management and counseling of affected individuals and their families. However, the advances in delineation and understanding have also identified major gaps in our knowledge. The following section identifies some of the problems remaining to be solved through basic research and clinical investigation.

"What is the nature of the genetic defects underlying the genetic heterogeneity in Gaucher disease?"

Clearly there are major phenotypic differences among the three subtypes of Gaucher disease. What is the nature of the molecular defects in each? What is the molecular pathophysiology of the neurologic manifestations in patients with Types 2 and 3 disease? From a genetic perspective, the markedly different phenotypes presumably are due to different structural gene mutations which result in differentially altered residual acid β-glucosidases. These classes of mutations may have different physiokinetic properties, but must share a common functional defect. It could be proposed that the gene has at least two functional domains and that mutations in one would alter the enzyme such that neurologic disease resulted. Mutations in other domains would result in an altered acid β-glucosidase, but no neurologic disease. Perhaps the Type 1 mutations occur in the nonneurologic domain and result in an altered Vmax for the residual activity as suggested by the studies of Pentchev et al (60). Other Type 1 mutations may exist that are K_m or stability variants.

Type 2 mutations occur in the neurologic domain, altering the gene such that the residual acid β-glucosidase cannot prevent the neurologic disease manifestations. Future characterization of the Type 2 enzyme may reveal altered physiokinetic properties and perhaps altered substrate specificities toward glucosyl ceramide and glucosyl psychosine. Type 3 mutations also would alter the gene in the neurologic domain, but the altered enzymes might be catalytically more functional than the Type 2 mutations, since the clinical manifestations in Type 3 are delayed and less severe.

As to the related question, the pathophysiology of the neurologic manifestations in Type 2 and 3 homozygotes—several possibilities come to mind. Perhaps there is insufficient *in vivo* activity, a "threshhold effect," so to speak, such that a certain amount of catalytic function is required to prevent neuronal disease. Perhaps the neurotoxicity is due to altered substrate specificity and resultant glucosyl psychosine accumulation, somewhat analogous to the pathophysiology in Krabbe's disease (61). Alternatively, it is possible that the accumulation of presently unidentified substrates causes the neuropathology. One or more of these possibilities may underlie the neuronopathogenesis.

"What is the molecular basis for the clinical variation in Type 1 variants from different ethnic groups?"

There is remarkable clinical heterogeneity among Type 1 homozygotes from different ethnic or demographic backgrounds. It is likely that these Type 1 variants represent allelic mutations which result in altered acid β-glucosidases with slightly different physiologic properties within the Type 1 or nonneurologic domain. Characterization of these properties may identify allelic differences permitting the recognition of genetic compounds (62) and, thereby, providing improved prognostic information.

> "What is the molecular basis for the *variable expressivity* among and within Type 1 Ashkenazi Jewish families?"

Possible explanations for the variable expressivity in Ashkenazi Type 1 disease might include one or more of the following. An increased rate of substrate or precursor synthesis may be the result of a glucosyltransferase or other enzyme polymorphism. The existence of alternate catabolic enzymes would also decrease the substrate load, perhaps an allelic polymorphism with a slightly lower K_m. Different turnover rates of cells containing substrate precursors; for example, leukocytes and erythrocytes. Or, different rates of excretion of substrate or precursors among individuals, etc.

> "What are the physiokinetic properties of normal acid β-glucosidase and what is the nature of the enzymatic defect in each of the Gaucher subtypes?"

With the artificial substrate used by most investigators, 4-methylumbelliferyl-β-D-glucopyranoside (4MU-Glc), two major β-glucosidase isozymes can be detected. The "acid" and "neutral" isozymes have been distinguished by their differential pH optima, substrate specificities, posttranslational modifications and subcellular localizations (63). The acid or lysosomal β-glucosidase is membrane-bound and/or extremely hydrophobic, requiring detergents to hydrolyze its primary natural substrate, glucosyl ceramide. In contrast, the neutral enzyme is soluble, does not bind to Concanavalin A, and does not cleave glucosyl ceramide. Only the acid isozyme is deficient in the various Gaucher subtypes. Although the neutral isozyme does not hydrolyze glucosyl ceramide, its abundance in most tissues can cause problems when determining the presence of minor acidic components and in heterozygote detection (see below).

A heat stable glycoprotein which binds to the acid isozyme was discovered in 1971 (39) and subsequently purified and characterized (64). However, the physiologic function of this molecule has not been determined. Does it serve as a stabilizing or catalytic cofactor for the enzyme in the lysosome? Is it needed for the enzyme to bind substrate more efficiently, or is it a membrane-bound component (although easily solubilized) which directs the proper insertion or orientation of the acid β-glucosidase active site in the membrane for optimal substrate binding and catalysis? Such information will require the characterization of the enzyme-effector interaction in artificial membranes, or perhaps in liposomes. These studies should provide important insights into the catalytic mechanisms of this, as well as other enzymes which are membrane-bound and/or hydrolyze lipid substrates. The hydrophobicity of the acid isozyme has contributed to the difficulties experienced in its purification and subsequent characterization. Further studies are required to characterize the properties of homogeneous (that is, silver stain pure) enzyme from normal and Gaucher sources. Such studies may provide information on the various enzymatic lesions among and within the Gaucher subtypes. In addition, the availability of large quantities of homogeneous enzyme for amino acid sequencing and antibody production is a prerequisite for the isolation and cloning of the structural gene for acid β-glucosidase.

> "What is the significance of the elevated acid phosphatase and angiotensin-converting enzyme activities?"

In addition to the deficiency of acid β-glucosidase in the tissues of Gaucher homozygotes, the levels of the nontartrate inhibitable acid phosphatase (31), angiotensin converting enzyme (65) and transcobalamin II (66) are elevated. Are these elevated proteins involved in the pathogenesis of the disease, are they a secondary effect of glucosyl ceramide accumulation or are they a measure of reticuloendothelial system activity? Might these enzymes indicate the degree of boney involvement and serve as prognostic markers of disease severity?

> "What are the physiologic effects of substrate accumulation?"

Glucosyl ceramide primarily accumulates in the lysosomes of the reticuloendothelial cells, as evidenced by the progressive hepatosplenomegaly and bone marrow involvement. However, it is not clear if the substrate deposition impairs reticuloendothelial function. The fact that patients have elevated immunoglobins, monoclonal gammopathies and various malignancies suggests that progressive substrate accumulation may be associated with immune and/or reticuloendothelial dysfunction. To date, the function of these systems has not been investigated or correlated with biochemical and clinical disease progression. For example, studies of macrophage-monocyte function, particularly of macrophage-mediated factors, have not been undertaken. Does substrate accumulation alter the function of these cells? Also, does substrate deposition in lymphocytes result in altered immunologic competence? Finally, questions related to the potential toxicity of glucosyl psychosine must be addressed. Is the rate of disease progression and occurrence of neurologic manifestations in the different subtypes correlated with their respective residual enzyme's ability to hydrolyze this compound? Glucosyl psychosine may be cytotoxic in small amounts, and may be responsible for functional impairment of visceral as well as neurologic cells. Determination of the glucosyl psychosine content in various tissues from Gaucher patients as well as *in vitro* exposure of cultured cells to this substrate may provide insight into the disease pathogenesis.

"Can a reliable assay be developed for discrimination of Gaucher heterozygotes? What is the carrier frequency for the Type 1 subtype?"

To date, a number of β-glucosidase assays have been reported for the identification of affected homozygotes and the heterozygous carriers of the disease-causing genes (53, 67–72). These assays use fibroblasts or leukocytes as enzyme source and either the artificial substrate, 4MU-Glc, or the natural substrate, glucosyl ceramide, which has been radiolabeled or fluorescently tagged. Experience with these assays has demonstrated their accuracy for homozygote diagnosis. However, discrimination of obligate heterozygous carriers has proven less reliable, except when cultured fibroblasts are used. Cultured fibroblasts and cultured amniotic cells are advantageous since they only express the acid and not the neutral β-glucosidase. Thus, diagnostic assays, particularly those measuring 4MU-Glc activity, are not complicated by the presence of the neutral isozyme. The major disadvantage in the use of these cells is the need to obtain a skin biopsy from each patient in order to establish a cell line. These procedures require a significant time-energy expenditure and are expensive, thus abrogating their routine use. Peripheral blood leukocytes, on the other hand, are easy to isolate and provide an adequate source of enzyme; their only disadvantage is that both the acid and neutral isozymes are present, making assays with artificial substrates less specific. Clearly, reliable assays are needed for heterozygote discrimination, especially for Type 1 disease. Perhaps the use of isolated lymphocytes or granulocytes and the natural substrate will provide the specificity, sensitivity and reliability required for carrier detection programs. With such assays, a more precise estimate of the frequency of carriers for Type 1 disease will be established. It is likely that programs currently screening for Tay-Sachs disease carriers in the Ashkenazi Jewish population would simultaneously screen for carriers of Gaucher disease. From such epidemiologic studies, the frequency of Type 1 disease among the Ashkenazim can be more accurately determined.

Finally, there are imminent questions relating to problems in management of disease complications and development of specific and efficacious therapy.

"Does splenectomy accelerate boney disease progression?"

The literature reflects a dichotomy. Reports from Israel (73) and the United States (74–76) suggest that total splenectomy results in an accelerated course of Type 1 disease. In particular, a rapid increase in liver size, increased skeletal deterioration and renal involvement. In contrast, groups in South Africa (77) and the United States (46, 78) have data which indicate no accelerated skeletal involvement, although they noted the hepatomegaly in patients with Type 1 disease. Swedish investigators (79, 80) correlate the occurrence of neurologic manifestations in Type 3 disease with splenectomy. Since there have been no prospective studies, it is difficult to evaluate these disparate results. One of our gaps in knowledge is the lack of information on the natural history (and its variability) of Type 1 disease. There have been no prospective studies of adequate numbers of patients to generate information on the disease course, its variability and complications. Only by carefully executed studies by a team of physicians expert in the hematologic, orthopedic, radiologic and genetic aspects of this disease can this information be collected and interpreted. Such studies are a prerequisite for improved patient care and management.

"Will enzyme replacement provide efficacious treatment?"

As discussed above, several investigators have attempted enzyme replacement in patients with Types 1 and 3 disease. Partially purified acid β-glucosidase has been intravenously administered directly (57) or entrapped in autologous erythrocytes (58) or liposomes (59). Biochemical evidence for substrate hydrolysis in liver, erythrocytes and plasma has been reported (57), but others could not confirm these findings (58). Multiple administrations of enzyme were not associated with an immune response, indicating the apparent safety of this approach. However, these studies have not demonstrated evidence for clinical improvement. Further studies, perhaps using purified acid β-

glucosidase modified in the oligosaccharide moiety to increase reticuloendothelial uptake, are needed to determine if enzyme replacement in Type 1 Gaucher disease is biochemically and clinically efficacious. In addition, improved methods of enzyme purification may be required for the frequent administration of adequate amounts of sterile, highly catalytic enzyme.

"Will alternative strategies prove therapeutic?"

Future prospects for the treatment of Gaucher disease include cellular and genetic engineering strategies. At the cellular level, bone marrow transplantation from a histocompatible donor may provide stem cells with normal acid β-glucosidase activity. Such cells could potentially repopulate the marrow and, following differentiation, also provide a source of Kupffer cells with active enzyme. The major barrier to the implementation of bone marrow transplantation, even with a histocompatible donor, is the high morbidity and mortality associated with this procedure. Perhaps when new methods are developed for crossing histocompatibility barriers and abrogating graft versus host rejection, bone marrow transplantation may become an effective therapeutic modality.

The rapid advances in recombinant DNA technology portend the future development of gene therapy for Gaucher disease. This strategy requires the isolation and cloning of the cDNA and genomic DNA for human acid β-glucosidase, formidable, but feasible undertakings. If the gene (cDNA) can be isolated and cloned, it is then conceivable that it can be used to produce large quantities of the human enzyme in bacteria or yeast for enzyme replacement. Or perhaps, the gene (genomic DNA) can be transferred into human cells (for example, the patient's bone marrow) using an appropriate viral vector. The availability of the canine analogue of Gaucher disease (81) will provide a model system in which to develop and evaluate these cellular and genetic strategies. Careful biochemical, cellular and genetic assessment of enzyme replacement, bone marrow transplantation, and gene transfer endeavors can be rigorously accomplished in the canine analogue prior to human trials.

In summary, the past century has witnessed the recognition and delineation of this disease entity. The characterization of the clinical, pathologic, biochemical, and genetic aspects of this disorder has provided important understanding of the disease pathogenesis and has set the stage for future investigation. It is anticipated that continued basic and clinical research will lead to the development of effective therapeutic and preventative modalities for the many patients and families suffering from this genetic disorder. Within this perspective, it is possible that the disease will be conquered within the next decade.

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Pancreatic Edema: Its Effect on the Function and Morphology of the Pancreas in Dogs and Rats

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Pancreatic edema is supposedly the first stage of acute pancreatic necrosis (1). On the basis of experiments, it is generally accepted that the active secretion of the pancreas against obstruction predisposes to development of acute pancreatitis. Obstruction of the outflow of pancreatic juice raises the pressure in the excretory duct system, disrupting ductules and acini (2) located behind the obstacle. The secreted digestive enzymes escape from the excretory duct system, get into the interstices of the gland and damage pancreatic acinar parenchyma and blood vessel walls (2). Even though this theory is accepted, we still do not know whether obstruction of the outflow of pancreatic juice influences the synthesis and secretion of pancreatic proteins, the activity of digestive enzymes in the glandular interstitial fluid during the early phase of pancreatic edema. Our study examined whether or not a self-defense mechanism does exist in the pancreas inhibiting the autodigestion of the gland induced by its own enzymes.

We followed protein synthesis by investigating the incorporation of [^{75}Se] methionine into pancreatic proteins, also the digestive enzyme activity in pancreatic interstitial (edema) fluid and formation of protein "plugs" in the pancreatic excretory ducts soon after the occlusion of the juice outflow induced by the ligation of main excretory ducts both in stimulated and resting pancreas in dogs and rats. Protein secretion in pancreatic juice after releasing the brief ductal occlusion was investigated, too.

Materials and Methods

Group 1: 70 male CFY rats with about 300 g b.w. were anesthetized with Nembutal, 58 of them were used for incorporation of (^{75}Se) methionine into pancreatic proteins. The common bile duct was ligated close to the duodenum in ten rats for 48 hours, in ten rats for 24 hours, and in 14 rats for three hours. Twenty-four rats served as controls. Each rat was given 10 μCi/100 g b.w. of (^{75}Se) methionine (radioactive concentration 18.5 MBq/ml, Akad. der Wissenschaft der DDR Ztr, Inst. für Kernforschung, Dresden) into the femoral vein. For half of the rats, it was given together with 4U/kg b.w. secretin + CCK-PZ (GIH Lab., Stockholm). After 20 min, the rats were exsanguinated from the abdominal aorta, the pancreas was removed, weighed and homogenized on ice. The proteins were precipitated with 10% trichloracetic acid and the precipitate was washed with 80% alcohol dissolved in concentrated formic acid. Radioactivity was measured in a Packard 5319 autogamma scintillation spectrometer and was expressed as cpm/mg protein. Protein was measured by the method of Lowry et al (3). Plasma radioactivity was expressed as cpm/ml. Plasma lipase (4) and amylase (5) activity was also determined.

The common bile duct of the remaining 12 rats was cannulated close to the duodenum and the duct was ligated at the hepatic hilum. Each rat received 4U/kg b.w. of secretin + CCK-PZ (GIH Lab., Stockholm) into the femoral vein. In six rats, pancreatic juice was collected for 180 min, then the same dose of secretin + CCK-PZ was given. After the second stimulus, juice was collected again for 60 min. Another six rats were stimulated as before, but the outflow of juice was obstructed for 180 min. Then the occlusion was released, and the rats received a second hormonal

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stimulus as previously described; then the juice was collected for 60 min.

The juice samples were weighed and the protein contents were measured by the method of Weichselbaum (6).

Group 2: Eighteen male dogs anesthetized by chloralose-urethane and 35 male CFY rats anesthetized by Nembutal were used. The dogs were subjected to laparotomy, the main pancreatic duct was cannulated and pancreatic juice was collected while stimulating the pancreatic function by giving 2U/kg b.w. of secretin and CCK-PZ (GIH Lab., Stockholm) for 60 min. Then the stimulation was stopped and, in eight dogs (17.6 ± 1.6 kg b.w.; mean ± SEM), the outflow of juice was obstructed to induce pancreatic edema. In five dogs (16.8 ± 1.5 kg b.w.), 10 ml of 5% sodium taurocholate was injected and in five further dogs (16.2 ± 1.4 kg b.w.) 10 ml of sunflower oil was injected intraductally to induce acute pancreatic necrosis. Pancreatic interstitial fluid was collected from each dog with a cotton wick introduced gently into the pancreatic interlobar spaces 30 and 90 min after obstructing the outflow of juice or inducing pancreatitis.

In the first group, pancreatic interstitial fluid was collected also at the 5th min after occlusion. The samples of pancreatic interstitial fluid were analysed for lipase (4) and amylase (5) activity as in the samples of pancreatic juice, and as in the arterial plasma samples taken before stimulating pancreatic secretion and 90 min after duct ligation or the induction of pancreatic necrosis. At this time, ascitic fluid was collected and analyzed in the same way. Histologic examination of the pancreas was performed. From the group consisting of 35 rats 26 received 2U/kg b.w. secretin + CCK-PZ (2U/kg b.w.) as a bolus into the femoral vein and bile pancreatic juice was collected for 20 min. Then in eight rats (261 ± 10 g b.w.) outflow of bile pancreatic juice was obstructed to induce pancreatic edema. In nine rats (279 ± 6 g b.w.) 0.2 ml of 5% sodium taurocholate and in nine further rats (272 ± 7 g b.w.) 0.2 ml of sunflower oil was injected intraductally to induce acute pancreatic necrosis.

Pancreatic interstitial fluid was collected with a cotton wick at the 180th min after duct ligation or induction of acute pancreatic necrosis. The rats were exsanguinated from the abdominal aorta so as the 9 (266 ± 4 g b.w.) unstimulated control rats. Plasma, bile, pancreatic juice, and interstitial fluid samples were analyzed for lipase (4) and amylase (5) activity. Histologic examination of the pancreas was performed. Statistical analysis of dogs and rats was performed after analysis of variance using Dunnett (7) contrasts.

Group 3. Ten male dogs (16.5 ± 1.8 kg b.w.) and 52 male CFY rats were anesthetized as in Groups 1 and 2. In six dogs, pancreatic function was stimulated by 4U/kg b.w. of secretin + CCK-PZ (GIH Lab., Stockholm) given into the femoral vein and pancreatic juice was collected for 60 min; the main pancreatic ducts were ligated in two dogs for 90 min, in two dogs for two hours and in two dogs for 24 hours. Four unstimulated dogs served as control. In three of them, the main pancreatic duct was ligated for the same periods as described before, while one dog was left completely intact. Pancreatic juice was weighed and analyzed for protein content (6).

Specimens from the pancreas were fixed in 4% formalin embedded in paraffin and 3−5 μm thick sections were cut from them. These were stained by haematoxylin-eosin and searched for intraductal protein precipitation ("plug") by using light microscopy.

Pancreatic function of 15 rats (283 ± 12 g b.w.) was stimulated by 2, 4 or 8U/kg b.w. of secretin + CCK-PZ given as a bolus into the femoral vein. Bile pancreatic juice was collected for 20, 40 and 60 min; 15 unstimulated rats (269 ± 12 g b.w.) served as controls. Bile pancreatic juice was weighed and protein level was measured (6). The pancreas of 22 male (267 ± 14 g b.w.) CFY rats was investigated histologically: pancreas of 2 intact rats was stimulated by 4U/kg b.w. of secretin + CCK-PZ given into the femoral vein. The pancreas was investigated histologically 20 and 60 min after pancreatic stimulation. Ten rats of this group got 4U/kg secretin + CCK-PZ into the femoral vein, the remaining ten rats served as unstimulated controls. In each rat the common bile duct was ligated and the pancreas of two rats was investigated histologically for 60 min, that of two rats for 90 min, of two rats for two hours, of two rats for three hours, and of two rats for 24 hours. The pancreas was fixed and examined histologically as before. The statistical analysis was performed after analysis of variance using Dunnett (7) and Dunn (8) contrasts.

Results

Group 1.: Ligation of pancreatic ducts, that is, induction of pancreatic edema increased the pancreatic weight and decreased incorporation of (^{75}Se) methionine into pancreatic proteins (Table I). In addition, it raised lipase and amylase activity in blood plasma (Fig. 1) regardless of the stimulation of pancreatic function. Stimulation of

TABLE I

Weight of Pancreas and Incorporation of [^{75}Se] Methionine into Pancreatic Proteins of Rats

Groups of rats	Body weight g	Weight of pancreas mg	[^{75}Se] methionine incorporation (cpm/mg protein)	%
Intact untreated (7)	352 ± 14	837 ± 51	301 ± 23	31 ±02
Intact stimulated (7)	346 ± 13	746 ± 62	288 ± 16	36** ±03
c b d ligated for 3^{hrs} (7)	358 ± 6	1099** ± 52	214* ± 32	24* ±04
Stimulated + c b.d. ligated for 3^{hrs} (7)	348 ± 11	1555** ± 87	355 ± 19	38** ±03
Intact untreated (5)	320 ± 22	985 ± 31	766 ± 97	60 ±08
Intact stimulated (5)	313 ± 10	797 ± 80	694 ± 46	51 ±04
c b.d ligated for 24^{hrs} (5)	332 ± 19	1245** ± 76	275** ± 56	17** ±04
Stimulated + c b.d. ligated for 24^{hrs} (5)	310 ± 19	1035** ± 91	295** ± 41	18** ±04
c.b d. ligated for 48^{hrs} (5)	336 ± 13	1164** ± 72	385** ± 20	21** ±01
Stimulated + c.b.d ligated for 48^{hrs} (5)	332 ± 12	1207** ± 100	341** ± 23	21** ±02

Incorporation of methionine 3, 24 and 48 hours after pancreatic ductal obstruction. Pancreatic function was stimulated by a pulse injection of 4 U/kg b.w. of secretin + CCK-PZ given into femoral vein. Values are mean ± SEM; number of rats in parentheses; c.b.d. = common bile duct; *$p < 0.05$, **$p < 0.01$ vs corresponding values of intact untreated group; %: cpm/mg pancreatic protein in % of cpm/ml plasma.

pancreatic function restored the decreased incorporation of labeled amino acid into the acinar parenchyma induced by a three-hour ligation of pancreatic ducts, but was ineffective, when pancreatic ducts had been ligated for 24 and 48 hours (Table I). The three-hour occlusion of pancreatic juice flow decreased the secretion of pancreatic proteins (Table II).

Group 2.: As expected, induction of pancreatic edema or experimental acute pancreatitis increased plasma lipase and amylase activity in dogs (Fig. 2) and caused a considerable increase in the activity of both enzymes in pancreatic interstitial fluid (Fig. 3). This activity was about 30% of that measured in pancreatic juice collected before the ligation of ducts. In the first 90 min of pancreatic edema activity of both enzymes remained unchanged in the pancreatic interstitial fluid, although in edema fluid due to acute experimental pancreatic necrosis lipase and amylase activity decreased (Fig. 4). In ascitic fluid concomitant to acute pancreatic necrosis, activity of lipase and amylase was found to be higher than in pancreatic interstitial fluid, when measured 90 min after induction of pancreatic necrosis (Fig. 4).

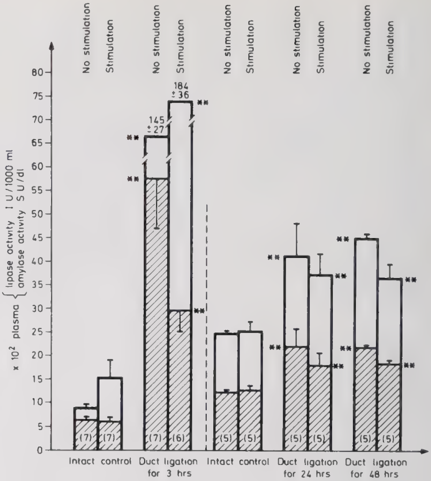

FIG. 1. Lipase and amylase activity in blood plasma of rats 3, 24 and 48 hours after ligation of common bile duct. Pancreatic function was stimulated by 4 U/kg b.w. of secretin + CCK-PZ. Values are mean ± SEM; number of rats in parentheses; ▨ lipase activity; ☐ amylase activity; $^{xx}p < 0.01$ vs corresponding intact control value.

In rats, both ligation of pancreatic ducts (common bile duct) and induction of acute experimental pancreatic necrosis raised lipase and amylase activity in blood plasma (Table III). Pancreatic edema as well as pancreatic necrosis caused considerable increase of lipase and amylase activity in the pancreatic interstitial fluid (Table III); this activity was about 20% of that measured in the juice collected before ligation of the common bile duct. In pancreatic edema focal necrosis of acini, in experimentally induced pancreatic necrosis extensive necrosis of the acinar parenchyma was observed.

Group 3.: In dogs, there is no measurable basal secretion. Stimulation of pancreatic secretion raised both protein concentration (20 ± 8 g/liter; n = 6) and protein output (402 ± 154 mg/60 min; n = 6) in pancreatic juice. In rats, each dose of hormones raised both protein concentration (Fig. 5) and protein output in bile pancreatic juice for 20 and 40 min periods in a higher level than in the corresponding basal juice. During 60–90 min protein plugs developed in the ligated pancreatic excretory duct system of dogs (Fig. 6). In stimu-

TABLE II

Flow of Pancreatic Juice and Its Protein Level Induced by Stimulation in Intact and Duct-ligated Rats

	1st stimulation of exocrine pancreatic function•		2nd stimulation of exocrine pancreatic function•		
	Collection of pancreatic juice for 180'		Collection of pancreatic juice for 60'		
	Flow ml/180'	Protein g/l	Flow ml/60'	Protein g/l	
Group A. (6)	0.30 ± 0.02	50.5 ± 5.0	0.22 ± 0.02	44.0 ± 3.5	p<0.05
Group B. (6)	Ligation of the common bile duct for 180 min.		0.17 ± 0.02	33.4 ± 2.5	

- • bolus of 4 U/kg b.w. of secretin + CCK-PZ given into fem. vein
- values are mean ± SEM
- ( ) number of rats

lated groups of rats intraductal protein plugs could be demonstrated, whether the pancreatic ducts had been not ligated (Fig. 7a) or ligated for about one to three hours (Fig. 7b). The stimulated acinar cells were vacuolized and their lumen was dilated. Three hours after pancreatic stimulation, most of the plugs disappeared, while in rats with ligated ducts, pancreatic edema became more and more striking. Edemic fluid was infiltrated by inflammatory cells, for example by leukocytes. The inflammatory interstitial reaction became more and more intensive. About 24 hours later vacuoles disappeared from the acinar cells and their luminal dilation stopped. The necrobiosis of acinar cells had started and finally the edema disappeared. Proliferation of fibroblasts was observed.

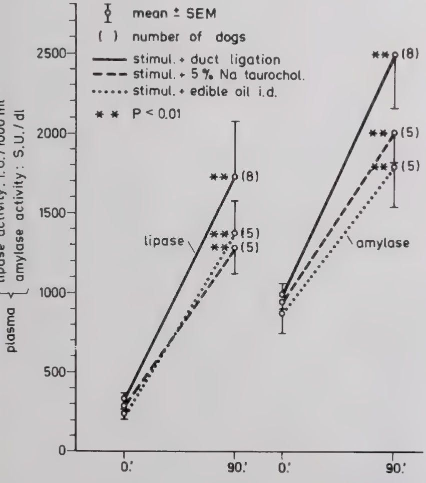

FIG. 2. Lipase and amylase activity in blood plasma of dogs 90 min after pancreatic ductal ligation or induction of experimental acute pancreatitis. In each group of dogs pancreatic function was stimulated by intravenous infusion of 2 U/kg b.w. of secretin + CCK-PZ given for 60 min.

Discussion

Pancreatic edema induced by the occlusion of the juice outflow increased the weight of the gland and raised lipase and amylase activity in blood plasma. Ligation of the excretory duct system caused decreased incorporation of (^{75}Se) methionine into pancreatic proteins showing that the ability of the acinar parenchyma for synthetizing pancreatic secretory proteins was decreasing when the outflow of pancreatic juice was occluded. In this case, the rising intraductal pressure may be the inducing factor. In other experiments, when saline was injected by pressure and in a retrograde way into pancreatic ducts incorporation of labeled valine into pancreatic proteins decreased, too (9).

In patients with pancreatic edema, a secretion

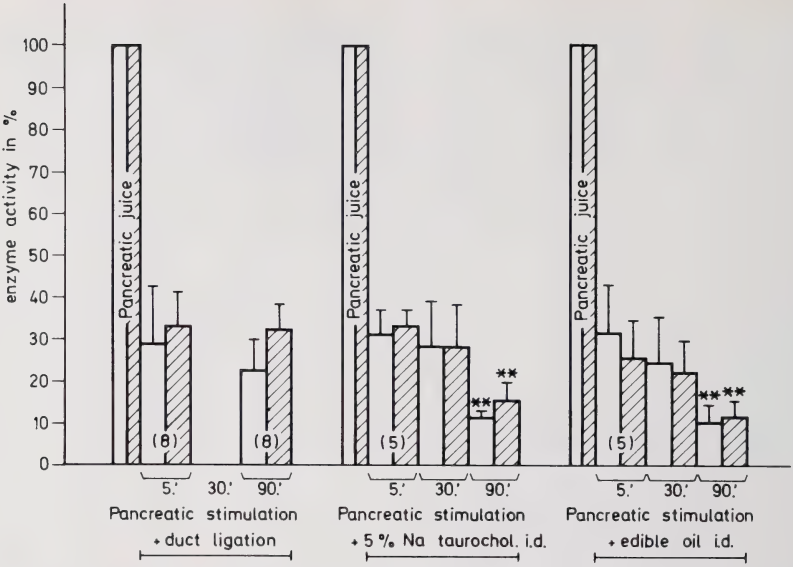

FIG. 3. Lipase and amylase activity in pancreatic interstitial fluid of dogs expressed in percentage of their activity in pancreatic juice collected before duct ligation or induction of pancreatitis. Values are from 5th, 30th and 90th min after induction of edema or acute pancreatitis and expressed as mean ± SEM; number of dogs in parentheses; ☐ lipase activity; ▨ amylase activity; $^{xx}p < 0.01$ vs corresponding 5th and 30th min activities.

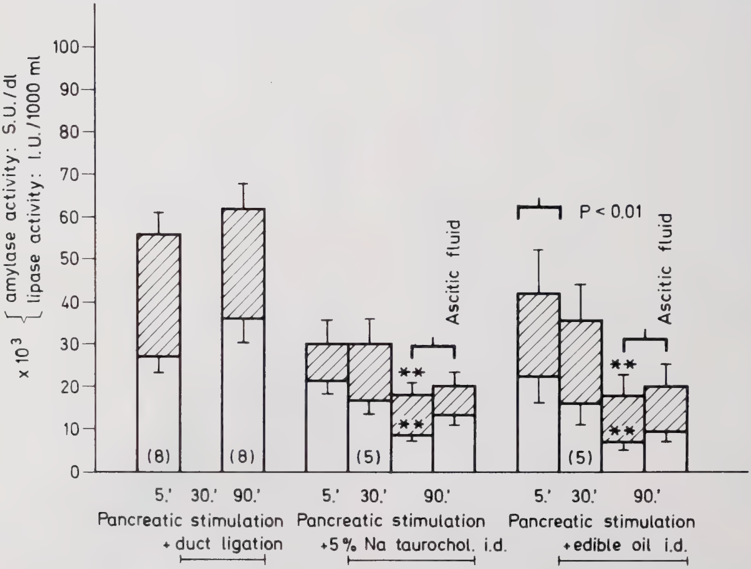

FIG. 4. Digestive enzyme activity in pancreatic interstitial and ascitic fluid of dogs after induction of pancreatic edema or acute pancreatitis. Values are mean ± SEM; number of dogs in parentheses; ☐ lipase activity; ▨ amylase activity; $^{xx}p < 0.01$ vs corresponding 5th and 30th min activities.

TABLE III

Lipase and Amylase Activity in Rats after Ligation or Induction of Acute Pancreatitis

		Plasma		Pancreatic interstitial fluid			
Groups	Body weight g	lipase I U/1000 ml	amylase S U./dl	lipase (x 10^3) I U/1000 ml	%	amylase (x 10^3) S U/dl	%
Intact rats	266 ± 4 (9)	282 ± 51 (9)	2473 ± 100 (9)	-	-	-	-
Ligation of c.b.d. + stim of pancr. secr	261 ± 10 (9)	1063 ± 180** (8)	7270 ± 872** (8)	44 ± 11 (8)	24 ± 7 (8)	134 ± 30 (7)	19 ± 5 (7)
Pancreatitis induced by sodium taurocholate	279 ± 6 (9)	1538 ± 164** (9)	8197 ± 1010** (9)	24 ± 3 (9)	14 ± 3 (9)	91 ± 8 (8)	12 ± 1 (8)
Pancreatitis induced by sunflower oil	272 ± 7 (9)	1656 ± 164** (9)	11190 ± 1751** (9)	25 ± 2 (9)	18 ± 3 (9)	156 ± 18 (7)	24 ± 3 * (7)

Activity in Rats 180 min after ligation of common bile duct or induction of acute pancreatitis. Values are mean ± SEM; number of rats in parentheses; c.b.d. = common bile duct; $^*p < 0.05$; $^{**}p < 0.01$ vs corresponding values of intact rats; %: expressed in percentage of bile pancreatic secretion taken as 100%.

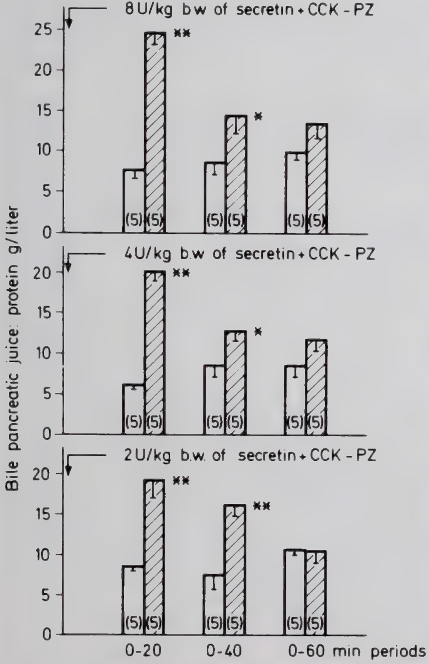

FIG. 5. Protein level in bile pancreatic juice of rats collected for 20, 40 and 60 min periods after pulse injection into femoral vein. Values are mean-SEM; ☐ basal value; ▨ stimulated value; number of rats in parentheses; $^xp < 0.05$, $^{xx}p < 0.01$ vs corresponding basal value.

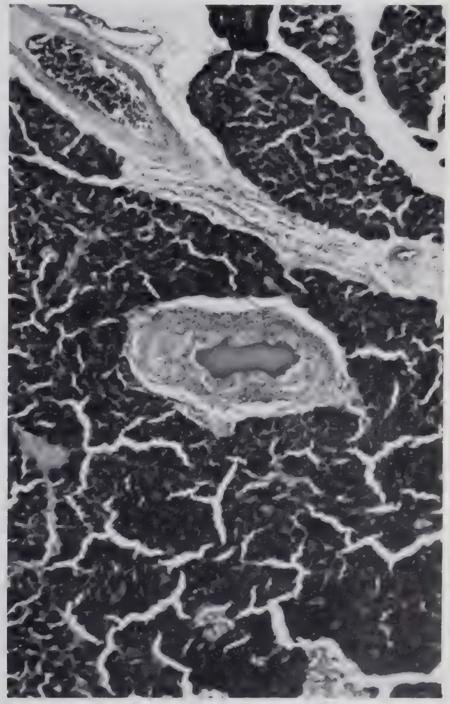

FIG. 6. Protein "plug" fills out pancreatic ducts lumen of a dog 90 min after pancreatic stimulation. Edema and infiltration of the interstitium by round cells can be observed (×100) (H.E.)

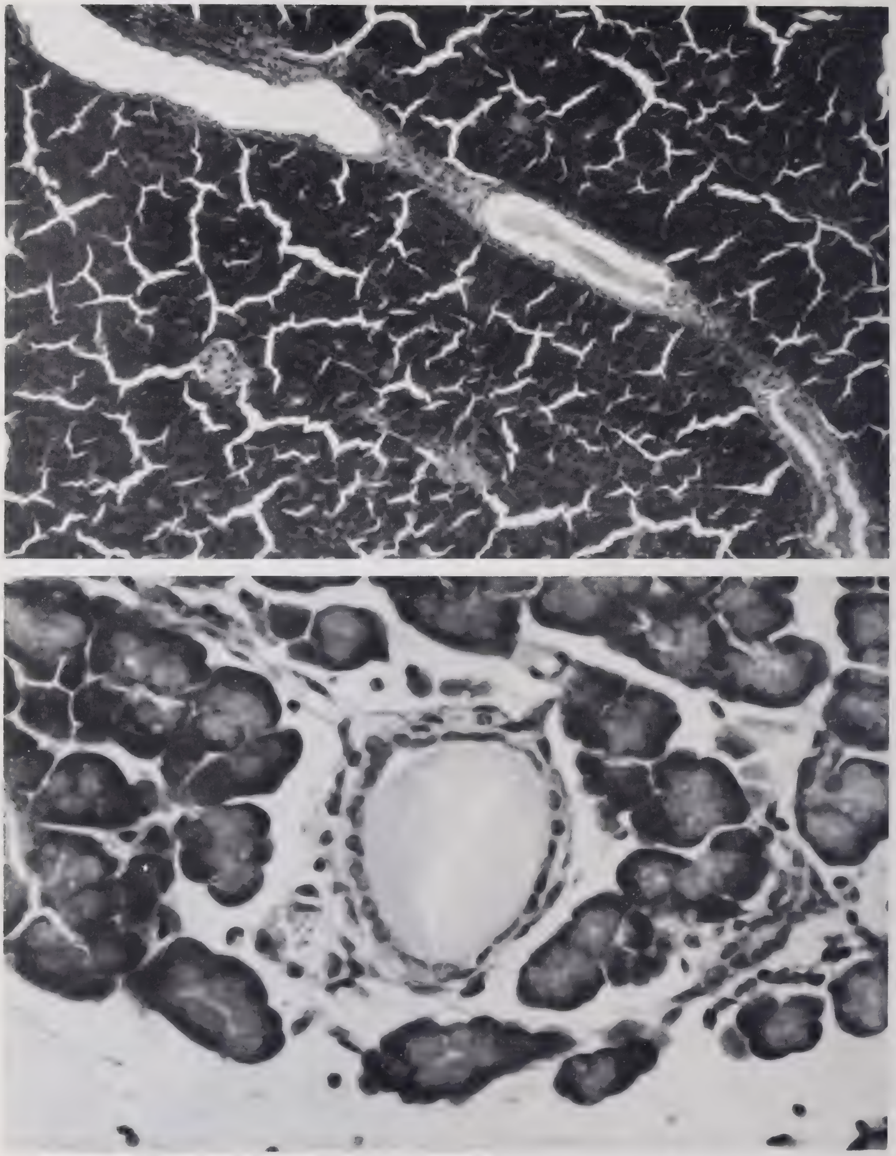

FIG. 7. *a* Protein "plug" fills out a smaller pancreatic duct's lumen of a rat 60 min after pancreatic stimulation by 4 U/kg b.w. of secretin + CCK-PZ (×150) (H.E.) and *b*, after pancreatic stimulation combined with ligation of the common bile duct for 120 min. In the interstitium edema rich in protein can be observed (×250) (H.E.)

response different from that of control subjects was found; their pancreatic secretion was characterized by low volume, low bicarbonate concentration and elevated enzyme activity (10). After releasing the obstruction, pancreatic tissue regenerated in a short time (11).

In our study, we have demonstrated that in rats the ability of acinar cells for secreting proteins (enzymes) is diminishing on a second stimulation, when before this second stimulation the outflow of pancreatic juice had been occluded. Stimulation of pancreatic function, however, can restore the protein synthetizing ability of acinar cells damaged by a three-hours occlusion of the pancreatic excretory duct system. The results discussed before may refer to the manifestation of an intrapancreatic self-defense mechanism in case the excretory system of the gland is occluded.

Occlusion of the pancreatic excretory duct system led to high enzymatic activity in pancreatic interstitial fluid. In dogs and rats the digestive enzyme activity in pancreatic interstitial fluid reached 20%−30% of that in stimulated pancreatic juice collected before ductal occlusion. In pancreatic edema of dogs enzymatic activity did not change in the interstitial fluid, while in experimental acute pancreatic necrosis it decreased in the first 90 min and increased in the ascitic fluid when compared to enzymatic activity in interstitial fluid.

In pancreatic edema, sporadic damage of the acinar parenchyma was found and the necrosis was focal. Experimentally induced acute pancreatic necrosis, however, led to extended and confluent necrosis of the acinar parenchyma. These suggest that pancreatic digestive enzymes are not the primary damaging factor in acute pancreatitis or pancreatic necrosis. The phenomenon can also be explained in another way; namely, in experimentally induced acute pancreatitis there is a continuous flux of pancreatic digestive enzymes from the interstitial fluid into the ascitic fluid and/or the enzymes in the pancreas are victims of the glandular selfdigestion. Other experiments in isolated perfused canine pancreas have confirmed our results. The increased secretory state of the pancreas did not appear to influence adversely the response of the gland to injury (12).

Supramaximal peptidergic or cholinergic stimulation of the pancreas, however, led to interstitial acute pancreatitis (13, 14). Vacuolization of acinar cells was also observed (13, 14). We observed the same also in acinar cells of rats after submaximal pancreatic stimulation by secretin + CCK-PZ.

In dogs and rats stimulation of pancreatic acinar parenchyma increased both protein level and output in pancreatic juice. *The intraductal protein "plugs" are protein precipitates and their formation and demonstration in histologic sections is due to the process of tissue fixation.* This process is essentially protein precipitation. Formation of intraductal protein "plugs" is the consequence of elevated protein level in pancreatic juice. This is reported in this study and has also been reported by other authors (15). Thus, we could demonstrate protein "plugs" both in unoccluded or in occluded pancreatic ducts of rats with stimulated pancreatic function. Under these conditions the difference we have found was that the protein "plugs" induced by occluded pancreatic ducts and stimulation of the gland were connected with pancreatic edema. Although, the more the edema advanced, the more the plugs disappeared.

Protein "plugs" could be demonstrated in long term alcohol feed, but also in one normal Wistar rat (15). In human pathology it is suggested that protein "plugs", that is, precipitations of a protein material in pancreatic ducts are to be regarded as the primary factor in chronic pancreatitis. The "plugs" are leading later to the occlusion of the pancreatic excretory duct system (16) mainly, when the "plugs" become calcified. In our experiments the "plugs" seemed to have a transient character, they disappeared about three hours after the ductal occlusion and/or stimulation of the gland. Moreover, the possibility cannot be excluded that "plug" formation in human pathology is consisting of at least three processes: one is leading to intraductal "plug" formation because of the high protein level in pancreatic secretion. The other as lactoferrin makes the protein precipitate insoluble (17) which might become calcified in the third step. On the basis of histologic sections, however, one cannot decide whether noncalcified protein "plugs" are consisted of physiologic or pathologic proteins regarding their origin and composition.

Summary

Effects of pancreatic edema induced either by pancreatic ductal occlusion or by pancreatic ductal occlusion connected with stimulation of the acinar parenchyma was studied in rats. Ductal occlusion of three, 24 and 48 hours significantly increased the gland weight but decreased incorporation of (^{75}Se) methionine into pancreatic protein. Stimulation of the pancreas in rats with ducts ligated for 24 and 48 hours was ineffective on the decreased (^{75}Se) methionine incorporation. A three-hours occlusion of pancreatic juice flow

caused a decrease in the secretion of pancreatic proteins on a second pancreatic stimulation given after releasing the ducts. The results suggest that pancreatic edema, or more precisely, ductal occlusion, induces changes in the pancreatic function which is acting as an intraglandular self-defense mechanism.

Pancreatic edema as well as experimentally induced acute pancreatic necrosis raised the digestive enzyme activity in pancreatic interstitial fluid of dogs and rats; it reached 20%–30% of the enzyme activity of stimulated pancreatic juice collected before ductal occlusion or induction of pancreatitis. In pancreatic edema of dogs, the enzymatic activity remained high and unchanged in the interstitial fluid during the first 90 min after ductal occlusion, in acute pancreatic necrosis, however, it decreased. In pancreatic edema focal necrosis of acini, in experimentally induced pancreatic necrosis extensive necrosis of the acinar parenchyma was observed. This may suggest that digestive enzymes per se may not be the primary damaging factor in acute pancreatitis. In dogs and rats graded doses of secretin + CCK-PZ increased protein level and output in pancreatic juice. Occlusion of the stimulated juice in dogs and rats, or pancreatic stimulation without ductal ligation in rats, led to intraductal formation of protein plugs. The plugs can be demonstrated by histologic examination for 120–180 min after pancreatic stimulation. The intraductal plugs disappear as edema advances in duct ligated rats.

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Effects of Intravascular Pancreatic Secretory Proteins on Pancreatic Secretion

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Abstract

The authors investigated whether or not pancreatic secretory proteins given into the blood circulation can increase protein level and output in the pancreatic juice of recipient animals. Fresh pancreatic juice was collected from donor dogs and rats and the juice was given intravenously to anaesthetized animals of the same species. Pancreatic juice was collected from each recipient animal by giving 1 U/kg b.w. of secretin intravenously and their pancreatic juice flow, protein, and enzyme secretion in juice was determined. Animals of the same species which had not received pancreatic juice served as control. Pancreatic secretory proteins given into the blood increased the protein level and output in pancreatic juice of dogs and rats. The results suggest that intravascular pancreatic secretory proteins may promote protein secretion in pancreatic juice.

Introduction

An interesting problem of pancreatic physiology is, whether pancreatic secretory proteins are lost or whether they are used again by the organism after completing their digestive action. It can be demonstrated that some of the pancreatic digestive enzymes such as chymotrypsin (1–3), elastase (4), lipase (5), and amylase (6) are reabsorbed from the intestinal lumen into the blood stream (7–8) and, when entering pancreatic interstices, they can be secreted by the pancreas (9). This process is the enteropancreatic circulation of pancreatic secretory proteins (7–8). Other authors confirm the enteropancreatic circulation of pancreatic amylase (10). In our study, we demonstrate that pancreatic secretory proteins given into the blood stream increase secretion of proteins into pancreatic juice in dogs and rats.

Materials and Methods

Mongrel male dogs and CFY male rats were used. Dogs were anaesthetized by chloralose (0.1 g/kg b.w.) rats by urethane (1.25 g/kg b.w.). Pancreatic juice was collected from donor dogs and rats the pancreatic secretion of which was stimulated by intravenously given 4 U/kg b.w. secretin + CCK-PZ (GIH Lab., Stockholm). Eighteen recipient dogs were subjected to laparotomy. Subsequently, a gastric fistula was prepared and the pylorus was ligated. The small pancreatic duct was ligated and a polyethylene cannula was introduced into the main duct. 1 U/kg/150 min secretin (GIH Lab., Stockholm) was given to each dog into the femoral vein using a Harvard infusion pump. Pancreatic juice was collected for 150 minutes in 30 minute periods. Arterial blood samples were taken every 30 min. After the second collection period 2.8 ml ± 0.7 ml/kg b.w. fresh canine pancreatic juice (that is, 19.7 mg ± 5.3 mg protein/kg b.w.) was given to nine dogs (18.2 ± 1.3 kg b.w.; mean ± SEM) as a bolus into the femoral vein. The other nine dogs (17.8 ± 2.6 kg b.w.) served as a control group and received physiologic saline in the same way.

Twenty recipient rats were subjected to laparotomy. The common bile ducts were ligated at the hepatic hilum and were cannulated close to the duodenum to collect pancreatic juice for 60 min. Each rat received 1 U/kg b.w. of secretin (GIH Lab.) given as a bolus into the femoral vein. Ten rats (300 ± 15 g b.w.) got fresh rat pancreatic juice (1 ml/kg b.w.) (that is, 48 ± 1.6 mg protein/kg b.w.). Ten rats served as a control (305 ± 9 g b.w.).

Pancreatic juice samples of donor and recipient dogs and rats were weighed. The lipase (11) and amylase activity (12) and the protein level (13) were measured in the juice of donor and recipient dogs as well as the lipase and amylase activity in

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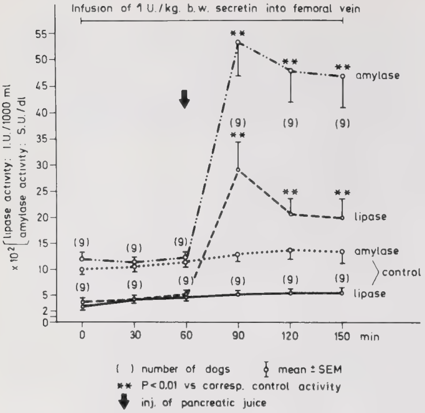

FIG. 1. Effect of pancreatic juice given into blood on the lipase and amylase activity in canine blood plasma.

plasma samples of the recipient dogs. Amylase activity and protein level were measured in the pancreatic juice of donor and recipient rats as well as the amylase activity in plasma samples of the recipient rats. Arterial blood pressure was measured every 30 min by using mercury manometer in dogs. The results were evaluated statistically by using "Student's" paired t test, or after analysis of variance Dunnette (14) and Dunn contrasts (15). The results are expressed as mean ± SEM.

Results

As it was expected, injection of fresh pancreatic juice into blood increased ($P < 0.01$) both lipase and amylase activity in the plasma of dogs (Fig. 1). Injection of pancreatic juice did not affect the pancreatic juice flow in recipient dogs though it increased the lipase and amylase activity and protein concentration ($P < 0.05$) of pancreatic juice when compared to the corresponding values prior to the injection of the juice. Injection of pancreatic juice increased protein output in the pancreatic juice of recipient dogs when compared to the corresponding value in the control group ($P < 0.01$) (Table I).

Injection of pancreatic juice increased amylase activity in blood plasma as well as protein concentration and output in the pancreatic juice of recipient rats (Table II). Other values did not change.

Discussion

It is not easy to explain the mechanism through which pancreatic secretory proteins that get into

TABLE I

Effect of Intravenous Fresh Canine Pancreatic Juice on Pancreatic Lipase and Amylase Activity and Protein Secretion in Dogs

Periods	I 0-30 min	II 30-60 min		III 60-90 min	IV 90-120 min	V 120-150 min
Control group (9) mean ± SEM						
Protein mg/liter	14644$^{\bullet}$ ± 2887	8156 ± 2335	Saline	10556 ± 3479	10089 ± 2267	10333 ± 2258
Protein mg/30′	51.3 ± 19.6	22.3 ± 5.8		26.5 ± 6.6	23.4** ± 5.3	20.1** ± 4.5
Lipase activity x 10^3 I.U/liter	287.6 ± 28.4	208.4 ± 45.6		210.5 ± 55.0	225.5 ± 56.3	226.4 ± 53.5
Amylase activity x 10^3 S.U/dl	432.7 ± 58.8	301.3 ± 54.6		304.1 ± 68.1	312.6 ± 66.7	325.5 ± 59.6
Pancreatic juice ml/30′	3.9 ± 1.1	3.8 ± 1.1		3.8 ± 1.2	3.1 ± 0.9	2.9 ± 0.9
Treated group (9) mean ± SEM						
Protein mg/liter	10511 ± 5190	5422 ± 1208	Pancreatic juice	8756 ± 2367	12567 ± 3350	15878* ± 5700
Protein mg/30′	44.4 ± 10.9	32.9 ± 6.8		32.1 ± 8.9	44.1 ± 10.4	45.0^{aa} ± 5.6
Lipase activity x 10^3 I U/liter	101.9^{aa} ± 36.3	87.1^{a} ± 30.0		150.5 ± 57.9	195.2* ± 58.2	174.8 ± 61.7
Amylase activity x 10^3 S.U/dl	201.9^{a} ± 65.7	162.0 ± 46.9		241.1 ± 82.5	298.7* ± 82.2	298.5* ± 81.7
Pancreatic juice ml/30′	6.6 ± 1.3	7.1^{a} ± 1.2		5.8 ± 2.0	6.0 ± 1.7	6.2 ± 1.7

• mean ± SEM ( ) number of dogs

a P< 0.05 compared to corresp value in the same period in control (saline) group

aa P< 0.01 compared to corresp. value in the same period in control (saline) group

* P< 0.05 compared to the corresp. value in the II. period in the same group

** P< 0.01 compared to the corresp value in the I. period in the same group

TABLE II

Effect of Intravenously Injected Fresh Rat Pancreatic Juice on Pancreatic Protein Secretion in Recipient Rats

		Control group (10)	Treated group (10)	
Plasma	Amylase S.U./dl	2391 ± 320.4	15336 ± 721.1	$P < 0.01$
Pancreatic juice	Flow ml/60 min	0.07 ± 0.01	0.08 ± 0.01	N.S.
	Amylase S.U/dl $\times 10^3$	554 ± 73	610 ± 79	N.S.
	Amylase output S.U/60′	374.9 ± 52.9	483.5 ± 84.6	N.S.
	Protein mg/l	14590 ± 1322	20030 ± 236	$P < 0.05$
	Protein mg/60′	1.01 ± 0.12	1.54 ± 0.18	$P < 0.05$

• mean ± SEM

( ) number of rats

the blood stream are able to stimulate the pancreatic acinar parenchyma to increase protein secretion. One of the possible explanations is that the injected secretory proteins enter the pancreatic interstices from the blood and from there they get into the acinar cells via basolateral membranes (16).

It can also not be excluded that the injected juice, as in humans (17–19), might contain some peptides affecting pancreatic secretion. The peptides in human pancreatic juice, however, are not stimulants for external pancreatic secretion. Moreover, the injected juice does not affect instantly canine pancreatic secretion. Consequently, this effect cannot be induced by peptides. In dog, the increased protein secretion was concomitant with increase in lipase and amylase secretion; in rat it did not exist. We have to mention that the mechanism described in this paper does not seem to be very effective from a biologic aspect. Namely about 3% (0.5 mg/rat) is secreted by the pancreas either from the injected protein (16 mg/rat) or from the intraacinar pooled protein due to the given protein.

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Hemodynamic Improvement after Percutaneous Transluminal Angioplasty

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Abstract

A group of 24 male patients underwent 33 percutaneous transluminal angioplasties of stenotic lesions at various sites. The iliac arteries were the most frequent site in this series followed by the superficial femoral arteries. Hemodynamic assessment was helpful in the follow up of these patients and is a good predictor of the end clinical result. Evaluation by radiographic appearance is not as accurate. Too aggressive dilatation may have a detrimental effect.

Introduction

The dilatation of atherosclerotic stenotic blood vessels in various locations began with work of Dotter and Judkins in 1964 (1). This procedure achieved little popularity in the United States until Gruntzig reported successful results with his technique of percutaneous transluminal angioplasty (PTA). He used a specially designed double lumen catheter in 1977 (2). This procedure has now achieved wide acceptance as another modality in the treatment of arterial occlusive disease. Most of the results of the procedure have been reported in terms of clinical improvement and radiographic improvement. There has been little data on the measurement of the hemodynamic changes following angioplasty. We are reporting our results using a comparison of the hemodynamic, radiographic and clinical results both before and after percutaneous angioplasty.

Materials and Methods

The results in series of patients who underwent percutaneous transluminal angioplasty in the past 24 months at the Bronx V.A. Medical Center in New York were reviewed. In addition to a clinical and radiologic evaluation, these patients also had a noninvasive assessment of limb perfusion. This was performed by segmental plethysmography with a pulse Volume Recorder (Life Sciences Inc., Greenwich, Ct) and blood pressures were obtained by doppler sonography of the distal pulses using pneumatic cuffs at the ankle level before and after angioplasty. A repeat hemodynamic assessment was obtained three, six and 12 months after the procedure and yearly thereafter.

The clinical assessment was recorded as either good or poor. A good result meant subjective improvement. A poor result meant that the patient felt worse or the same as predilatation. The radiologic results were scored as poor, fair, or good based on the subjective evaluation of the radiologist.

The decision regarding treatment with percutaneous transluminal angioplasty was made by a vascular surgeon in conjunction with the vascular radiologist. All of the patients received aspirin, 300 mg, twice a day for two days prior to the procedure and for two days following the procedure. The arterial punctures were performed according to the usual Seldinger method (3). Usually the ipsilateral site was used for the arterial puncture, but at times the contralateral site was used. Heparin (5000u) was given intravenously or intraarterially after a diagnostic arteriogram was obtained. Metallic markers were placed on the skin at the level of the diseased artery to aid in the fluoroscopic localization of the lesions during the angioplasty. When arteries more distal than the common femoral artery were dilated 60 mgs of papavarine and 40 mgs of lidocaine were injected into the femoral artery. A guide wire was advanced beyond the stenotic region in the usual manner and then the Grüntzig balloon catheter was advanced over the wire. The balloon was positioned in the stenotic area and the guide wire

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was then removed. The balloon was inflated with radiopaque solution for 30 seconds on two occasions. A repeat angiogram under fluoroscopic control was performed to evaluate the effectiveness of the dilatation.

To have a uniform baseline for the noninvasive hemodynamic evaluation, the pulse volume amplitudes in the postoperative period were corrected according to the same brachial pressure and pulse rate as in the preoperative recording.

$$\text{Pulse volume} \propto \text{Systolic blood pressure (BP)}$$

$$\propto \frac{1}{\text{Pulse rate (PR)}}$$

$$\text{PV} \propto \frac{\text{BP}}{\text{PR}}$$

$$\text{Pulse volume}_2 = \text{Pulse volume}_1 \frac{\text{BP}_2}{\text{BP}_1} \cdot \frac{\text{PR}_1}{\text{PR}_2}$$

1 = preoperative
2 = postoperative

The hemodynamic evaluation was determined by measuring the pulse volume recordings at the ankle, calf and thigh and by calculating the ankle-brachial blood pressure rations. Twenty three patients had complete hemodynamic studies before and after PTA. The paired student T-test was used for a comparison of the ankle-brachial ratio and of the PVR amplitude at the level of the thigh, calf and ankle in these patients.

Statistically significant differences in this group, as determined by the paired student T-test of the ankle-brachial ratios, meant that the ankle-brachial ratio increased by 0.2 or more. This is the 95 percent confidence limit of the study population.

Results

There were 24 patients, all males 52 to 71 years of age, treated with percutaneous transluminal angioplasty. Diabetes mellitus was found in 58 percent, smoking in 79 percent, hypertension in 75 percent of these patients.

The most frequently treated lesion was in the iliac artery, followed next by the superficial femoral arteries. Other lesions were treated as shown in Table I. Indications for PTA are shown in Table II.

Three of the patients had more than one stenotic lesion requiring treatment. Three patients required repeat percutaneous transluminal angioplasty on a different occasion. In all three of this latter group, a decrease in the hemodynamic parameters measured by the pulse volume recording device was apparent prior to the repeat angioplasty.

TABLE I
Anatomic Locations of Percutaneous Transluminal Angioplasty

Renal artery	2
Iliac artery	12
Common femoral artery	1
Superficial femoral artery	7
Deep femoral artery	2
Tibioperoneal trunk	3
Posterior tibial artery	1
Saphenous vein graft for femoral popliteal bypass	2
Outflow tract of A-V fistula for hemodialysis	3
TOTAL	33

Location of stenotic lesions treated

There were 33 procedures performed in 24 patients. Two patients required vascular reconstruction after PTA because of lesions other than those treated by the PTA. There was one patient who was not successfully dilated. Evaluation by radiographic, clinical and hemodynamic parameters are listed below.

Radiographic vs Clinical Results

The radiographic appearance after PTA was characterized as poor, fair and good. Eleven lesions had a good radiographic result, 14 lesions had a fair result and eight had a poor result. All of these patients were also evaluated clinically. All showed immediate clinical improvement. The clinical results at the end of the observation period were graded as either poor or good. In all, ten patients were believed to have a poor clinical result and 23 to have a good clinical result. A comparison of the clinical vs. radiographic interpretation of the same patients is demonstrated in Diagram I.

The ankle-brachial ratio (Fig. 1) had increased from 0.49 ± 0.06 to 0.73 ± 0.06 ($p < 0.001$) in the immediate postoperative period. The ankle-brachial ratio remained significantly increased up to six months. At one year, there was not a

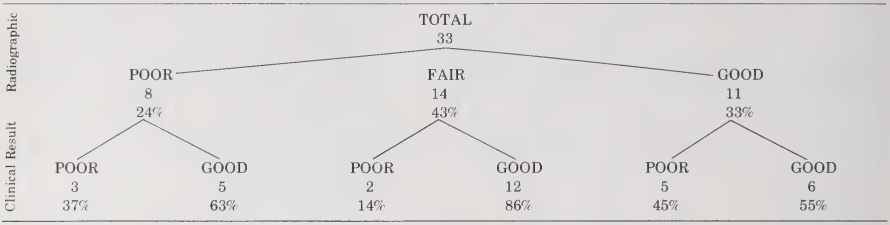
TABLE II
Symptomatic Indications for Percutaneous Transluminal Angioplasty

Claudication	8
Ulcer with or without gangrene	10
Rest pain	3
Inadequate flow in vascular access	2
Hypertension	1
TOTAL	24

Clinical symptoms of patients treated

DIAGRAM I

RADIOGRAPHIC vs. CLINICAL RESULT



A comparison of the clinical vs radiographic interposition.

significant difference in the ankle-brachial ratio from the preoperative evaluation.

The pulse volume amplitude immediately following dilatation (Figure 2a, b, c) increased significantly from 14.9 ± 1.6 to 20.9 ± 1.7 mm ($p < 0.001$) in the thigh, 9.6 ± 1.3 to 17.1 ± 2.3 mm ($p < 0.05$) in the calf and 5.6 ± 0.8 mm ($p < 0.01$).

When the ankle-brachial ratio increased more than 0.2 it was classified as a significant improvement. All patients had immediate clinical improvement but some subsequently regressed. Clinical results at the end of the observation period (one month to two years) were graded as either poor (unimproved) or good (improved) as shown in diagram II.

In the group with significant improvement of the ankle-brachial ratio and pulse volume, all eleven had good clinical results. In the patient group that had no significant improvement in ankle-brachial ratio, seven of twelve (59%) had a good clinical result. Of these seven, four had improvement in pulse volume amplitude. Only three

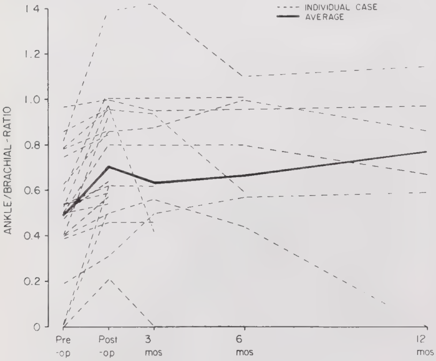


FIG. 1. Ankle-brachial ratio in preoperative and postoperative periods.

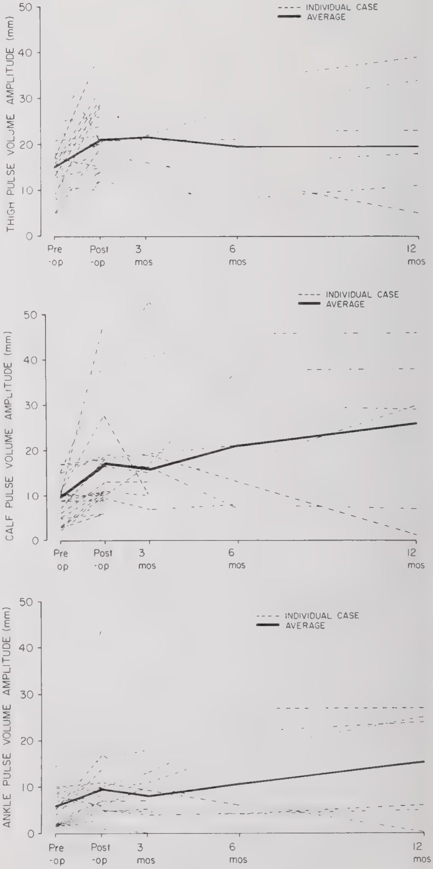
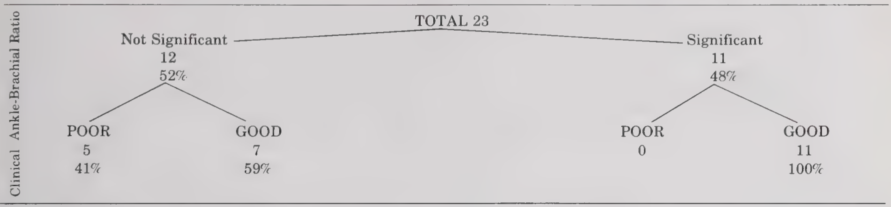


FIG. 2. Pulse volume amplitude in preoperative and postoperative periods.

DIAGRAM II

ANKLE-BRACHIAL RATIO vs. CLINICAL RESULT



A comparison of the clinical vs hemodynamic measurements.

patients, therefore, had good clinical results without objective hemodynamic improvement.

Discussion

From the comparison of the radiographic and hemodynamic evaluation of these patients, our results indicate that the utilization of the noninvasive hemodynamic parameters is a better indicator of the long term clinical results. In all of our patients who showed significant hemodynamic improvement, there was also a significant clinical improvement until the end of the observation period.

In contrast, the radiographic appearance of the dilated artery was not always a reliable indicator of success. In the group evaluated as having a "good" radiographic result, only 55 percent had clinical improvement at the end of the observation period. The group judged as "fair" in the radiographic assessment, however, showed 86 percent having a good clinical improvement. Therefore, it may be that an over aggressive dilatation actually has a detrimental effect. Block (4, 5) has studied animal and human pathologic changes in vessels after transluminal angioplasty and found that transluminal angioplasty often causes splitting and disruption of the atherosclerotic plaques and the underlying media. The degree of splitting depended upon the relative diameters of the stenotic lesion and the inflated balloon. Our findings indicate that aggressive dilatation may produce hypertrophic scarring at the site of dilatation or predispose to thrombosis events which may in the long term offset the initial improvement. The 54 percent good long term clinical results in our group with "poor" radiographic results may be explained by the theories of blood flow through stenotic vessels. Since flow changes relative to the fourth power of the radius of a vessel, a small change in the radius can result in a considerable change in flow (6). A ten percent difference in vessel calibre would be extremely difficult to observe radiographically but would allow a significant increase in flow. Furthermore, smoothing out of a rough stenotic area may significantly reduce the turbulent flow in a stenotic vessel (7, 8). This would improve the flow without actually changing the apparent diameter.

In the twelve patients who had no improvement in their ankle-brachial ratio, 59 percent had a good clinical result. This may be explained by calcification in the vessel walls which gave a false high ankle-brachial ratio which precluded a significant hemodynamic improvement following dilatation. In these cases the change in pulse volume amplitude may be a better indicator of improvement.

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Observer Error in Biopsy Interpretations and Outcome in Chronic Hepatitis

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Abstract

To assess the effect of inter- and intra-observer error on the diagnosis of chronic hepatitis, we reexamined liver biopsy slides from 30 patients whose biopsies were obtained more than five years ago. Each slide was reviewed on two separate occasions, without knowledge of previous diagnoses, by three pathologists from two hospitals. Patient outcome was assessed using a telephone questionnaire. Intra-observer agreement ranged from 83% to 96%. The two pathologists from the same hospital agreed 90% of the time, but over-all, the three pathologists disagreed on 27% of the slides ($P < .01$). Four of the original 30 diagnoses were unanimously reversed. This study confirms the benign prognosis of chronic persistent hepatitis compared to chronic active hepatitis, but emphasizes that interobserver variability reduces the predictive value of a single biopsy report. This has serious implications with regard to choice of therapy.

Introduction

The diagnosis of chronic hepatitis is largely based on histologic criteria in liver biopsy specimens. It is conventionally divided into several categories independent of the presence of cirrhosis, particularly chronic persistent hepatitis (CPH) and chronic active hepatitis (CAH) (1). CPH is assumed as a rule not to progress to cirrhosis while a significant number of patients with CAH progress to cirrhosis, particularly if not treated. Accurate diagnosis is important to reassure patients with CPH, and to at least consider immunosuppressive or antiviral treatment in some patients with CAH (2).

Materials and Methods

To assess the degree of reproducibility of diagnoses, three pathologists from two affiliated institutions were asked to review 30 liver biopsy slides from patients originally diagnosed as having chronic hepatitis, without knowledge of the clinical data. Each slide was assessed twice, the second observation one month after the first. The slides were assessed for the presence of piecemeal necrosis, fibrosis, and inflammation and assigned a diagnosis, if possible, of CPH, CAH and/or cirrhosis. It was thus possible to measure both intra- and inter-observer error. The slides came from patients of Dr. Fenton Schaffner. Ten patients with the original diagnosis of CPH and 20 with CAH were chosen. The dates of the biopsies ranged from 1967 to 1975, six to 14 years before follow-up information was obtained. The patients' ages ranged from 11 to 62 years at biopsy; 15 were female, 15 were male, HBsAg was present in five, absent in 20, and unknown in five.

The analyzing and reporting of observer variability is complex when three pathologists are making three possible diagnoses on two occasions. To simplify analyses, we assumed that CPH would require no specific treatment, and CAH

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TABLE I
Inter- and Intra-observer Error
(% Agreement)

	Pathologist		
	I	II	III
Pathologist I	84	73	73
II		93	93
III			91
Over-all agreement 73%			

TABLE III
Proportion Read as CAH/Cirrhosis

Pathologist	I		II		III	
reading	1	2	1	2	1	2
	.53	.43	.60	.63	.57	.60

Over-all $X^2_5 = 11.23$ by Cochran's Q test ($P < .05$)
Each reader is internally consistent ($P > .05$)
Reader I vs. II & III $X^2_1 = 8.03$ ($p < .005$)

and/or cirrhosis would, at least in antigen negative patients, lead to serious consideration of immunosuppressive therapy, or antiviral agents, in the case of HBsAg+ patients. Therefore, we post-hoc dichotomized the decisions of the pathologists into the categories requiring only symptomatic treatment, CPH, and that suggesting consideration of specific treatment, (CAH and/or cirrhosis).

Follow-up was determined by reviews of available records and by telephone interviews with patients not recently seen. All living patients were contacted. The cause of death was determined by clinical evaluation of the seven dead patients. Living patients were classified into those who felt well but might have nonspecific symptoms, and those who had specific symptoms and/or physical findings suggesting the diagnosis of chronic active hepatitis or cirrhosis.

Results

Intra- and inter-observer variability were slight with regard to description of such items as piecemeal necrosis and fibrosis. Differences arose when these were compiled into final diagnoses. Intra-observer agreement rates were 84%, 93%, 91% for the three pathologists (Table I). The agreement of Pathologist I with Pathologist II or III was 73%, but Pathologist II with Pathologist III was 93%. The over-all agreement rate among the three pathologists was 73%.

All of the observers agreed on the diagnoses of CAH ± Cirrhosis 16 times and on CPH six times for a total of 22 agreements, or 73% (Table II). Two out of three pathologists agreed that CAH/Cirrhosis was present on two more slides, and CPH was present in six more cases. Agreement was analyzed by the Cochran's Q test (3). Each reader was internally consistent. However, there was a significant difference at the .05 level when comparing the readings between observers. This is due to Observer I disagreeing with both Observers II and III. Observer I did not commit himself to diagnosis in eight of 30 cases. Observers II and III are from the same institution, while Observer I is from an affiliated institution.

TABLE II
Inter-observer Agreement by Diagnosis

	3/3	2/3	Total Patients
CAH ± Cirrhosis	16	2	18
CPH	6	6	12
	22	8	30

When the consensus diagnoses on the reviewed slides were compared with the original diagnoses on which therapy may have been based, some discrepancies were noted (Table IV). Three CAH patients were renamed CPH, while one CPH was reclassified as having CAH.

Of the 18 patients with reclassified CAH/Cirrhosis six were doing well, five had clinical complications, and seven had died (Table V). All contacted CPH patients had a benign course. Three patients had an initial diagnosis of CAH and a later clinical course more suggestive of primary biliary cirrhosis (PBC); one was classified as PBC on review, one as a possible cirrhosis, and the third as nonspecific reactive hepatitis or CAH.

Cumulative survival at six years was 75% of the CAH group and 100% of the CPH group. At nine years cumulative survival was down to 63% of CAH patients but still 100% for CPH patients. Of the seven who died (Table VI), four died of liver disease, two died of myocardial infarction, and one died in an accident. One of the patients who

TABLE IV
Original Compared with Consensus Diagnosis

		Consensus Diagnosis		
		CAH	CPH	Total
Original Diagnosis	CAH	17	3	20
	CPH	1	9	10
	Total	18	12	30

died of liver disease died from complications of primary biliary cirrhosis.

Discussion

In this study, no attempt was made to correlate therapy with morphologic features and outcome because the use of steroids depended as much on the course as on histologic appearance, and there was no way to separate cause and effect factors. Also, the numbers were too small to correlate the HBs antigen status with morphologic features and outcome.

The follow-up information was limited in scope and the numbers too small to draw firm conclusions about the prognostic predictability of the morphologic diagnoses. However, the results agree with previous findings that the prognosis of CAH is worse than that of CPH and that CAH and PBC may be confused histologically.

These data are in reasonable agreement with the other published studies in which inter-observer and intra-observer errors in liver biopsy specimens were assessed in a blinded fashion (4–6). In this study, the pathologists generally agreed on what they saw and the differences were mainly interpretative ones. Of the three pathologists, two work in the same institution and one of those trained the other. The third was trained and works independently, and it is not surprising that the differences were somewhat explained by these factors.

Although the intra- and inter-observer variability was not excessive, it and the discrepancies with the original pathologic diagnoses suggest the need for routine measurement of duplicate variability—especially if important clinical decisions are to be based on the conclusions. In addition, whenever observer error is more than 10% to 15%, it is important to control observer bias by arriving at a diagnosis from looking at the slide without knowledge of the clinical history or interpretations of previous biopsies. A second diagnosis can then be made after the additional information has been obtained.

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TABLE V
Outcome by Consensus Diagnosis

	Benign	Clinical Complications	Dead	Lost	Total
CAH and Cirrhosis	3	4*	4**	0	11
CAH	3	1*	3*	0	7
CPH	11	0	0	1	12

* One patient in each group later diagnosed as PBC
** Two patients died of myocardial infarction

TABLE VI
Deaths

Diagnosis	Age at Biopsy	Gender	Follow-up Time in Yrs.	HB_sAg Status	Cause of Death
1. Cirrhosis	54	F	9	–	Liver
2. Cirrhosis + CAH	62	M	6	–	MI
3. Cirrhosis + CAH	43	F	6	+	Liver
4. Cirrhosis + CAH	37	F	6	Unknown	MI
5. CAH	34	M	1	+	Accident
6. CAH → PBC	51	F	9	Unknown	Liver
7. CAH	18	M	1	+	Liver

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Smoke and Chronic Gastritis

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The pathogenic correlation between smoking and chronic gastritis is still today a matter of question. Edwards and Coghill in 1966 demonstrated the occurrence of chronic gastritis in more than 40% of the studied subjects smoking more than twenty cigarettes a day (1). On the contrary, further experiences of Wolff and a wide literature review collected by Vilardell, failed to confirm a close relationship between smoking and chronic gastritis (2, 3). Moreover, the association between smoking and bile reflux from duodenum towards the gastric lumen is well stated. At the same time, it is well known about the high incidence of antral gastritis in duodenogastric bile reflux (4, 5).

The aim of this work is to perform a statistical evaluation of the relationship between smoking and chronic gastritis, correlating the obtained data with the age of subjects and with the occurrence of duodenogastric reflux.

Materials and Methods

The studied subjects totalled 67. Thirty of them were non-smokers (NS) of which 21 were males and nine were females. Their mean age was 48 years, ranging in age from 21 to 78. Nineteen subjects were light smokers (LS) (five to ten cigarettes/day). Thirteen LS were males, six females. The mean age was 52 years, ranging from 22 to 81 years. The remaining 18 patients were heavy smokers (HS) (more than 20 cigarettes/day). Within this third group, 13 were males and five females. The mean age was 45 years, ranging from 20 to 76 years (Table I).

None of the studied cases had a high consumption of alcohol: subjects drinking more than 30 g/day of alcohol were excluded from the study.

A systematic study of the upper digestive system (oral cholecystography and endoscopy) was made in all cases, to exclude the presence of circumscribed lesions. Three were the fundamental endoscopic pictures considered: normal mucosa, congestive gastritis (zonal or diffuse redness of the mucosa, erosions, spontaneous hemorrhages, fragility) and atrophic gastritis (thin, gray-rose mucosa with possible evidence of vascular network, and/or erosive hemorrhagic phenomena). Furthermore we evaluated the presence of bile reflux.

During endoscopy, three bioptic specimens were taken of fundic mucosa (two along the lesser curvature and one on the greater curvature of the gastric body), and two of antral mucosa (on the anterior and posterior wall, within two centimetres from the pylorus). The bioptic specimens were fixed in formalin, embedded in paraffin and the sections cut 5 μ thick, orthogonally to the mucosal surface, and stained with haematoxylin and eosin.

The histologic diagnosis of chronic gastritis was done according to Cheli's classification, considering superficial gastritis (SG), interstitial gastritis (IG), preatrophic gastritis (PG), and atrophic gastritis (AG) (6). The SG is characterized by normal thickness of the glandular parenchyme, with increased lymphocytes in the surface epithelium and rich plasmacellular infiltrate in the interfoveolar areas (6, 7). Interstitial gastritis presents zonal lymphocyte infiltration localized in the interglandular interstitium, with normal glandular parenchyme. Preatrophic gastritis is characterized by reduction of the glandular parenchyme with inflammatory infiltrate extended to all the chorionic thickness. Atrophic gastritis presents marked reduction or even disappearance of the glandular tubuli, intestinal metaplasia of the surface epithelium and rich chorionic inflammatory infiltrate with plasmacellular prevalence (6, 7).

The obtained data were statistically analysed by means of the χ^2 test.

Results

Endoscopic findings: In the fundic area of nonsmoking subjects, normal mucosa was found

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TABLE I

Age Distribution of 67 Subjects in Relation to Their Smoking Habits

AGE	Nonsmokers	Light smokers (5−10 cig.)	Heavy smokers (>20 cig.)
20−50 years	17	10	12
>50 years	13	9	6

in 23 out of 30 cases (76.6%), congestive gastritis in three (10%), and atrophic gastritis in four (13.3%). Similar findings were observed in the fundic area of LS and HS (Table II).

The examination of antral mucosa in the NS group revealed the presence of normal patterns in 23 subjects (76.6%), of congestive gastritis in four (13.3%) and of atrophic gastritis in three (10%). These data failed to demonstrate significant differences when compared with what was found in LS, while, in HS, there is a significant decrease of normal patterns and a significant increase of congestive gastritis when compared with both the other two groups (Table III).

Evidence of duodenogastric bile reflux is present in two out of 30 NS (6.6%), in one out of 19 (5.3%) LS and in 13 out of 18 HS (72.3%): this value is significantly higher than the one observed in both NS and LS (Table III, IV).

Histologic findings: In the fundic mucosa, the smoking habit does not influence the incidence of chronic gastritis, since both LS and HS fail to demonstrate significant differences when compared with nonsmokers (Table V).

The analysis of the antral mucosa, in nonsmokers, shows normal findings in 14 cases (46.7%), superficial gastritis in seven (23.3%), preatrophic gastritis in five (16.6%) and atrophic gastritis in four (13.4%). In the LS group, the findings do not differ from those found in NS, while in HS a significantly higher frequency of preatrophic gastritis and atrophic gastritis is seen (Table V).

When related to age (subjects younger or older than 50 years) the frequency of chronic fundic gastritis shows increased values of preatrophic and atrophic gastritis in the older subjects of each group (Table VI). In the antrum, we find an increased frequency of preatrophic and atrophic gastritis in HS (either of the younger or of the older group) when compared with NS and LS (Table VI).

TABLE II

Endoscopic Fundic Findings in Subjects with Different Smoking Habits

ENDOSCOPY	N.S.† (30 cases)	L.S.† (19 cases)	H.S.† (18 cases)
Normal	23(76.6%)	14(73.7%)	12(66.6%)
Congestion	3(10%)	2(10.6%)	4(22.3%)
Atrophy	4(13.4%)	3(15.7%)	2(11.1%)

† N.S. = Non smokers; L.S. = Light smokers; H.S. = Heavy smokers

TABLE III

Endoscopic Antral Findings in Subjects with Different Smoking Habits

ENDOSCOPY	N.S.† (30 cases)	L.S.† (19 cases)	H.S.† (18 cases)
Normal	23(76.6%)	14(73.7%)	7(38.8%)
Congestion	4(13.4%)	3(15.7%)	10(55.6%)
Atrophic gastritis	3(10%)	2(10.6%)	1(5.6%)
Bile reflux	2(6.6%)	1(5.3%)	13(72.3%)

† N.S. = Non smokers; L.S. = Light smokers; H.S. = Heavy smokers.

Discussion

The analysis of our endoscopic data demonstrates a significantly higher incidence of congestive gastritis in antral mucosa of heavy smokers, while no differences are seen in the fundic area when smoking and nonsmoking subjects are compared. Of great interest, in this respect, is the frequent observation of duodenogastric bile reflux in the HS group (72.3% of total cases).

Histologically, the global evaluation of our data demonstrates a greater incidence of preatrophic and atrophic antral gastritis in heavy smokers, while no differences are found between nonsmokers and light smokers. The higher frequency of major antral lesions (preatrophic and atrophic gastritis) in heavy smokers appears to be independent of age since it is found in increased percentage both in people younger and older than 50 years (Tables VII, VIII).

Therefore, a first possible conclusion is the fre-

TABLE IV

Comparison between Endoscopic Antral Findings and Bile Reflux in 18 Heavy Smokers

ENDOSCOPY	BILE REFLUX Present	BILE REFLUX Absent
Normal	3	4
Congestion	9	1
Atrophic gastritis	1	—

TABLE V

Chronic Gastritis Incidence in Light (L.S.), Heavy (H.S.) and Nonsmoking (N.S.) Subjects

	FUNDUS			ANTRUM		
HISTOLOGY	N.S.	L.S.	H.S.	N.S.	L.S.	H.S.
Normal	15	9	11	14	7	5
	50%	47.8%	61.3%	46.7%	36.8%	27.7%
Superficial	8	5	2	7	6	2
gastritis	26.7%	26.2%	11.1%	23.3%	31.8%	11.2%
Preatrophic	2	3	2	5	3	5
gastritis	6.7%	15.6%	11.1%	16.6%	15.7%	27.7%
Atrophic	5	2	3	4	3	6
gastritis	16.6%	10.4%	16.5%	13.4%	15.7%	33.4%
N. of cases	30	19	18	30	19	18

TABLE VI

Chronic Gastritis Incidence in Relation to Age in 67 Subjects with Different Smoking Habits (Light Smokers = L.S.; Heavy Smokers = H.S.; Nonsmokers = N.S.)

		FUNDUS			ANTRUM		
AGE	HISTOLOGY	N.S.	L.S.	H.S.	N.S.	L.S.	H.S.
20–50	Normal	11	6	9	10	5	4
years		64.7%	60%	75%	58.8%	50%	33.3%
	Superficial	4	2	1	4	3	2
	gastritis	23.5%	20%	8.3%	23.6%	30%	16.7%
	Preatrophic	0	2	1	3	1	3
	gastritis	—	20%	8.3%	17.6%	10%	25%
	Atrophic	2	0	1	0	1	3
	gastritis	11.8%	—	8.3%	—	10%	25%
	N. of cases	17	10	12	17	10	12
> 50	Normal	4	3	2	4	2	1
years		30.8%	33.3%	33.3%	30.8%	22.2%	16.7%
	Superficial	4	3	1	3	3	0
	gastritis	30.8%	33.3%	16.7%	23%	33.4%	—
	Preatrophic	2	1	1	2	2	2
	gastritis	15.4%	11.2%	16.7%	15.4%	22.2%	33.3%
	Atrophic	3	2	2	4	2	3
	gastritis	23%	22.2%	33.3%	30.8%	22.2%	50%
	N. of cases	13	9	6	13	9	6

TABLE VII

Incidence of Major Gastric Lesions (Preatrophic and Atrophic Gastritis) in Relation to Smoking Habits (N.S. = Nonsmokers; L.S. = Light Smokers; H.S. = Heavy Smokers)

	FUNDUS			ANTRUM		
HISTOLOGY	N.S.	L.S.	H.S.	N.S.	L.S.	H.S.
N. of cases	30	19	18	30	19	18
Normal	15	9	11	14	7	5
	50%	47.3%	61.1%	46.6%	36.8%	27.7%
Major	7	5	5	9	6	11
lesions	23.3%	26.3%	27.7%	30%	31.5%	61%

TABLE VIII

Major Gastric Lesions (Preatrophic and Atrophic Gastritis) in Relation to Age and to Different Smoking Habits (N.S. = Nonsmokers; L.S. = Light Smokers; H.S. = Heavy Smokers)

		FUNDUS			ANTRUM		
AGE	HISTOLOGY	N.S.	L.S.	H.S.	N.S.	L.S.	H.S.
20–50	Normal	11	6	9	10	5	4
years		64.7%	60%	75%	58%	50%	33.3%
	Major	2	2	2	3	2	6
	lesions	11.7%	20%	16.6%	17.6%	20%	50%
	N. of cases	17	10	12	17	10	12
>50	Normal	4	3	2	4	2	1
years		30.7%	33.3%	33.3%	30.7%	22.2%	16.6%
	Major	5	3	3	6	4	5
	lesions	38.4%	33.3%	50%	46.1%	44.4%	83.3%
	N. of cases	13	9	6	13	9	6

quent finding of chronic antritis and of biliary reflux in heavy smokers. This observation appears even more interesting when we consider that these lesions were found in young people (under 50 years), but are quite rare in general population.

The present experience would confirm the possible pathogenetic role played by smoking on antral mucosa, realized with the mediation of bile reflux. In effect, previous experience of Aste and Molinari demonstrated the presence of chronic gastritis in 83% of subjects with bile reflux with a constant antral involvement and high frequency (50%) of isolated antritis (4).

On the contrary, the study of the fundic mucosa excludes every possible correlation between chronic gastritis and smoking. In effect, the frequency and type of gastritis are similar both in nonsmokers and in light or heavy smokers, the most severe lesions being strictly linked to the patient's age in all the three groups (Table VIII).

In conclusion, heavy smoking favors the development of chronic antritis inducing a duodenogastric bile reflux; on the contrary evidence of the possible influence of smoking on the inflammatory state of the fundic mucosa are missing.

Summary

The chronic gastritis incidence has been evaluated in 67 subjects with different smoking habit: 30 of them were nonsmokers, 19 were light smokers (from five to ten cigarettes/day) and 18 were heavy smokers (more than 20 cigarettes/day). Endoscopy demonstrated a higher incidence of congestive gastritis in antral mucosa of heavy smokers; no differences were seen in the fundic area when comparing smoking and nonsmoking subjects. In addition, heavy smokers showed evidence of duodenogastric bile reflux in 72.3% of total cases. The histobioptic analysis demonstrated in the antrum a greater incidence of preatrophic and atrophic gastritis in heavy smokers, when compared with nonsmokers and light smokers, while the incidence of chronic fundic gastritis did not differ among the three considered groups, being the most severe lesions strictly linked to the patient's age in all the cases. In conclusion, heavy smoking is frequently associated with chronic antritis, inducing a duodenogastric bile reflux; on the contrary evidence for a possible influence of smoking on the inflammatory state of fundic mucosa is missing.

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A Random Sample for Management and Planning: Social Research at The Mount Sinai Hospital

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Introduction

At The Mount Sinai Medical Center, the Department of Community Medicine considers the hospital itself a critical part of the "community." In accordance with departmental policy of technical assistance to community groups (1), Community Medicine developed an Office of Applied Social Research, specifically for research within the hospital. Much of the work in this office is in collaboration with the Vice-President for Planning and Management Information Systems.

A major feature of this collaboration is the selection of an annual 10% random sample of patients taken from different hospital computer files. The sample data are merged into a hierarchical dataset accessible by computer for analysis. The analysis is geared toward questions relevant to hospital management and planning. With this system, a great deal of information can be developed at relatively little cost.

Historical Background

Historically, computers were introduced into the hospital to facilitate financial functions. Consequently, most hospital computer files were developed in accordance with billing and reimbursement procedures. They were arranged in serially organized files to account for hospital services delivered to patients. These files were organized "almost on a one-to-one basis, between an application program's logical file and the physical data structure" (2). In other words, a data set was used in a program designed for a specific purpose. Neither files nor programs were easily adaptable to modification. Linking data in one file with those in another was even more problematic.

In the 1970s, data base management software became available, initiating a reduction of the close linkage between program and data. These systems featured multiple keyed data which were accessible through the use of English-like query languages. Keys could be used to extract subsets of the data quickly and efficiently. Although these systems were more flexible than simple raw datasets, flexibility was still too limited for analysis to be easily performed. Furthermore, the data base management system is expensive to install (3) and its advantage of speed not particularly significant in the analysis environment.

Aside from data set design, there is the problem of enormous volume in the various hospital data files.

> Because of economies, it is no surprise that enormously large quantities of data are being stored via computer. . . . Unfortunately, storing vast amounts of data in computer-based memory by no means automatically provides . . . access to the data so that meaningful information can be generated in an acceptable manner. When information cannot be produced from a data base, the value of the data, which is the raw material for the organizational commodity called information, is greatly diminished. (4)

The combination of data design problems and volume of data leads to a "waste" of data and a lack of information.

At Mount Sinai, we apply sampling techniques to the vast volume of data in different files to annually merge selected items for the establishment of an integrated dataset. We then access data from this set with highly flexible software programs. This permits the social scientists to study and manipulate the data with analytical methods to produce a wide range of organizational information.

Using a Sample

Hospital planning and management are often concerned not with the individual patient, but with the organization of the hospital itself. Using an approach developed in the social sciences, we employ a sampling procedure to select data about hospital patients that reflects the characteristics of a population of patients who use the hospital in a particular period of time (5). We take a 10% random sample of all Mount Sinai Hospital patients who use the hospital services in a given year. Appropriate demographic and utilization data are selected from different files and organized in a hierarchical structure on a single tape to provide an integrated dataset. This has been done each year since 1976.

To make information useful for the analyst and meaningful to the planner, every single item on the various hospital files needs careful assessment for both its integrity and its relevance to the study of the organization.

The question of data integrity usually rests with its use in a given department. Data which are used in a measure of accountability are usually accurate—those which are not are unreliable. For instance, date of discharge is accurate because the hospital must account for its billing of the length of stay. The discharge service is not as accurate. If a patient is admitted into one service and transferred to another one, it is expected that the service will be changed in the data input. However, it is not the kind of information which is required in any transaction. As a consequence, there are no management controls to insure an accurate updated data entry. The category "discharge service" is not as reliable as "date of discharge."

To assess the relevance of data, the question must be asked: can it be used for an indicator or not? To decrease cost, reduce volume, and facilitate manipulation of the data files, only items that can be used as indicators of essential variables are kept. For example, to bill a patient, the hospital needs a patient's full name. For purposes of analysis, we need only a unique number to identify the patient. To address a patient by mail, we need a full street address. For analysis, we may classify residents in various zip code areas as "poor," "middle income," or "upper income." The zip code becomes an indicator for types of residential areas.

Once we have selected our indicators, we can combine them in a variety of ways. We may decide to examine 1) the number of annual clinic visits serviced by a particular clinical service, 2) the inpatient types (private, semiprivate, etc.) serviced by those services, and 3) the distribution of lengths of stay in different inpatient services. These three variables can be combined to create an index of residents' workload. Over time, the index may be modified by adding other indicators or replacing some. The ways in which all these various indicators relate to each other as variables is the subject of social research (6).

To adapt the data in our sample for analysis, we select specific demographic and utilization items from the different files. Because the 10% sample reduces the volume of the data, it permits the merging of data from different files onto a single tape. The random sampling insures the integrity of relations between data elements and, at Mount Sinai, 10% of the patients are sufficient to insure a high degree of reliability. Using the patient as the unit of selection in contrast to visits or discharges, permits interrelation of the data to reflect the population of hospital users. For instance, we can ask how many patients account for what proportion of discharges. The data are linked through the use of the patient's identification number, a number unique to the patient throughout the hospital. Using files with a hospital-wide cutoff date, for example year-end, insures a consistent and fixed data base for analysis.

Selecting the Sample

To select the sample, we chose ten two digit random numbers by a random iterative process (7). We then took all patients whose identification numbers ended in those selected random numbers. (Every patient who uses the hospital has a unique identification number of seven digits. The numbers are given out in sequence to patients. Thus all the identification numbers end in a recurring series of two digit numbers ranging from 00 to 99. When we select ten pairs of numbers from the 100 possible pairs, we have ten percent of every 100 patients who use the hospital in a given year.) This design results in patient defined data that reflect the proportion of visits and discharges from different types of patients. In 1981, our 10% patient sample estimated the total number of outpatient visits made to be 30,803. This compares with the outpatient billing figure of 308,881. The estimate is within .03 percent of the actual figure.

The size of the sample depends, of course, on the size of the hospital. For purposes of understanding the relations between variables, the 10% sample at Mount Sinai Hospital is more than adequate. The ten percent sample was chosen following a procedure in which we explored two, five percent samples. Although there was no difference in the findings between the two, five percent samples, we needed a sufficiently large number of cases to enable us to perform multivariate analyses (8). The ten percent sample provides approximately 7,000 outpatients and 3,000 inpatients each year. With these data, we are able to conduct survey studies, a crosssectional picture of patients, visits and discharges. Since the same two digit numbers are pulled every year, we are also able to conduct studies with a longitudinal or panel design that permits the study of process from year to year in a time series (9). The ten percent sample enables us to link the various kinds of data about patients into a single flexible dataset from which we can relate such items as the patient's age to his length of stay and his residence to his use of the Emergency Room. We have also developed classifications of patients according to the type of utilization that has occurred.

The combination of variables which creates the classification becomes a new variable. These new data are entered into the dataset. Thus, from our sample we can not only combine existing variables, but we can create new data from them. These, in turn, become accessible for further investigation.

The 10% sample creates a new and flexible dataset with which to study the factors related to different issues for planning. The dataset is new because it combines elements from different files into a single dataset; flexible because the dataset is constructed and accessible for use in numerous software programs, applicable for social research, unlike business information files which are constructed for specific purposes and constrained for analysis by constant updating.

Uses of Data

How are data used to develop information for planning and decision-making? In addition to integrating information around the patients on an annual basis, we have begun to develop an historical base. From such an historical base we can study trends in patient populations and their utilization patterns. We can merge data on the same patients in different years to study the "process" of change in patient utilization and the "types" of patients who return as opposed to those who do not. As the census data become available, we can relate them to the residence of our patient population and initiate relatively inexpensive market studies.

The data available in the sample permit us to study problems at different levels of the organization for planning and management purposes. This is an important feature for the organization because the nature of the issues is very different from one level of the organization to the next.

Executive management, for instance, knows the annual costs and income from all outpatient visits; they also know the source of different amounts of outpatient income according to different methods of payment. However, they do not readily know the amount of inpatient income generated from different types of outpatients because the data are kept in different files.

Using the sample, we can provide information on the proportion of outpatients who become inpatients. We have further refined categories of outpatients by classifying them according to pay status, residence, and utilization patterns. These classifications are then related to inpatient admissions and methods of payment.

Operational management wants to determine optimal staffing patterns for patient demand, or to locate the bottlenecks which are a source of long waiting times. In the Emergency Room, for example, it is important to assess the most appropriate staffing patterns for the different levels of demand by day of week and hour of day (10).

Both executive and middle management problems can be addressed as applied research questions using the integrated dataset and the methods and techniques of social research. One study, for instance, looks at demand by type of utilization. From this study, it becomes clear that a small proportion of patients use a fairly high proportion of services. These "high demand, high cost" patients warrant further study. Another question raised is how the composition of inpatients changes in a given period of time. How consistent or variable are their demographic characteristics and sources of entry into the organization? What are the characteristics of the hospital census; how is it affected by holidays? How much of a geriatric population does Mount Sinai have? These and a wide variety of other questions and issues become accessible to study.

Analysis of the Data

The professional social science staff is essential to the appropriate use of the data to develop information by analyses. We emphasize the use of the data for analysis because various administrative staff can surely create special reports, based on the kinds of accountability for which they are responsible. However, when a new question or a new issue arises, it often has many ramifications and implications for treatment of the data beyond the knowledge and training of administrative or other professional staff.

Sometimes data do not form any pattern appropriate for planning. At such times, it can be helpful for the administrator to have documentation of this fact. For instance, the fluctuation of discharges appears to be so random that there is no pattern fine enough to predict their daily behavior. If the hospital has a "full-bed" policy, necessary for fiscal management, then inevitably "full-bed" implementation applied to such widely fluctuating changes in the number of discharges will result in some days when not all the patients can be admitted as planned. Since these days cannot be anticipated and controlled, then priorities for admission need to be reviewed and set by the appropriate authorities. The issue for the problem of planning admissions moves from one of better management when better management is not feasible to one of priorities for planned admissions. It also raises the importance of continuing study and possible development of a better management information system.

Discussion

Today, at least 80% of the hospitals have some computer capacity. In the larger teaching hospitals particularly, the volume of data available in computer files is enormous. These files are in the jurisdiction of different departments and consequently designed for different purposes. It is possible to extract data from these files and to use them as a source of information for a better understanding of hospital operations. Generally, however, programs need to be written specifically for each study in order to define and check the data required and to apply statistical operations to the selected data appropriate to the problems and issues at hand. The cost of producing such studies becomes inordinately high, whether the study is done inhouse or by a shared service. Furthermore, a new data base is established each time a study is undertaken, increasing costs. As far as we know, no hospital has attempted the approach of taking a 10% sample from various annual fields and merging them to link the data. We have found only one citation in the literature in which an ambulatory care practice uses a sample to produce routine reports (11). What we are emphasizing is the miniaturization of the data and making it accessible for many studies through selection of a sample. The sample is drawn once, variables defined and data cleaned. It is then accessible as a regular operational feature for use by social scientists to perform "secondary analyses," that is, analyses on data that are not collected for a particular purpose or study.

To implement the drawing of the sample and to produce pertinent information through application of analytical methods to the data, a research office must be composed of persons with different skills. The Office of Applied Social Research at Mount Sinai Hospital has a staff of two academically trained and experienced social scientists who conceptualize the problems brought to them into research terms. One research assistant works with both social scientists. The staff is completed with two programmers who are trained to work with several different datasets and to produce new datasets. They use some standard software packages and, in addition, do their own programming to respond to table requests from the social scientists.

The inhouse research staff develops an understanding of the highly complex organizational structure of the hospital and the medical school as a result of knowledge accumulated from a series of studies. Because these studies have been concerned with different areas of the hospital, an inhouse social scientist acquires a broad based sense of the interactions among hospital departments. (S)he also has an opportunity to learn the problems of the organization in response to its environment, and becomes aware of its functioning at the executive levels as well as the effect of executive decisions on the staff who come into contact with the patients.

Social science expertise as well as knowledge of the organization are both necessary ingredients to produce careful, sophisticated studies designed to respond to the need for information around a particular problem. Accessing sources of data through use of a sample permits a reasonably fast response. A social science staff on salary for purposes of research into the organization is a relatively unbiassed and effective resource because it is not caught up in any single operational area of the hospital. It is as such that it is partially supported by Mount Sinai Hospital rather than by any particular operational department.

Various aspects of the studies which have been done at The Mount Sinai Hospital will be presented in this journal focusing on the questions and issues which brought them about. Some of these questions have centered around the effect on Mount Sinai Hospital of the changing demands for health care in its community. Did the closing of so many hospitals in the New York area increase the demand for outpatient services? Among which types of patients? Would this entail a financial loss and in which area of the hospital?

Another set of questions arose as a result of the trend toward increased visits to the Emergency Room. What were the implications for the staff in the Emergency Room? Are the patients more seriously ill; did admissions increase? Does the increase result from patients coming to the Emergency Room instead of the clinics or are there more new patients?

In general, each particular study answers certain questions and raises new ones, leading to a sequence of issues and studies. It is this process of study and application as a cumulative effort that we feel contributes to the continued development of organizational information and understanding of process.

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The Role of Internal Sphincterotomy

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Abstract

Seven hundred and fifty patients underwent internal sphincterotomy between January 1972 and December 1980. The indications for this procedure were anal ulcer in 550 patients and hemorrhoids with constipation in 200 patients. The majority of patients were satisfied with the procedures, having relatively less pain and faster wound healing. The flatus incontinence or fecal soiling were seen in 16 patients and recurrences in two with the overall success rate of 97.6%.

Thus, internal sphincterotomy is a preferred modality for the treatment of anal ulcer and beneficial for patients with hemorrhoids with constipation.

Lateral internal sphincterotomy for anal ulcer has gained popularity and favor over conventional posterior sphincterotomy. The rationale of internal sphincterotomy is to lower the resting anal pressure and facilitate relaxation of the internal sphincter during defecation. In recent years, it has also been applied to various other conditions. That is, hemorrhoids with constipation, anal stenosis and megacolon, or ultrashort segment of aganglionosis. We have adopted its uses to anal ulcer and hemorrhoids with constipation and have obtained gratifying results.

Materials and Methods

From January 1972 to December 1980, 750 patients underwent lateral internal sphincterotomy; 380 males and 370 females, ranging in age from 20 to 78, with a mean of 40 years. The indication for this procedure was limited to chronic anal ulcer in 550 cases and 200 patients who had hemorrhoids with constipation. (Table I).

Among the 550 cases of anal ulcer, 434 (79%) ulcers were located at the posterior midline, 68 (12.4%) were anterior (55 of these patients were female), 40 (7.2%) both posterior and anterior (23 were female), and eight (1.4%) were located in other areas. Most of the operations were performed with spinal or general anesthesia although a few were done with local anesthesia. 550 anal ulcer were treated with lateral subcutaneous internal sphincterotomy (1, 2) and managed the co-existing conditions accordingly as listed in Table I.

Two hundred patients who had hemorrhoids associated with constipation are subjected to hemorrhoidectomies as well as internal sphincterotomies simultaneously.

Results

Since the extent of surgery differed depending on the pathology, the results varied. Most of the 550 anal ulcer patients were satisfied with the procedure since they had prompt relief from pain. Complete would healing took place within three weeks, except for seven patients who took longer to heal. Twelve patients experienced minor complications of gas or liquid incontinence, 12 had bleeding, nine complained of persistent pain or burning, four had infections, one, a fistula, and recurrences occurred in two patients. Most of the patients with minor complications improved as time went on, three of the 12 bleeding patients required surgical intervention. The nine patients who had pain and burning stated, however, that it was far less than before surgery. The one fistula patient and the two patients with recurrences underwent reoperations with good results.

The 200 hemorrhoidectomy-with-internal sphincterotomy group presented slower wound healing than the simple sphincterotomy group and took three to six weeks. Occasionally the sphincterotomized site exhibited delayed healing

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TABLE I

Type of Lesion and Operative Procedures

LESION	PROCEDURES	NO. OF PATIENTS
Ulcer	Sphincterotomy only	150
	Sphincterotomy and	
	Excision sentinel pile	227
	Excision external hemorrhoid	88
	Fistulectomy	48
	Excision papilla	37
Hemorrhoid with constipation	Sphincterotomy with Hemorrhoidectomy	200
		750

and eight of them took more than two months to attain complete healing. There were minor complications in four patients, bleeding in two, two had persistent pain, one had an infection, and one had a fistula; all of these patients responded to conservative treatment or minor operations. Recurrences have not yet been encountered up to date.

Discussion

The majority of anal ulcer patients have been satisfied with posterior internal sphincterotomy because of prompt pain relief. However, minor complications such as flatus incontinence or fecal soiling are rather high with an incidence of 8% to 50%. These complications have been lessened considerably by using lateral subcutaneous internal sphincterotomy with the incidence of 0 to 12% (Table II) (1, 2, 6–15).

Some investigators prefer anal dilatation over the surgical approach for anal ulcer (16). Whatever the treatment, the objective is to lower resting anal pressure. Since the advent of manometric studies, it has been clearly demonstrated that resting anal pressure is higher in patients with anal ulcers or hemorrhoids than normal subjects (17–19). Since 75% of resting anal pressure depends on the internal sphincter (20), it is necessary to divide the internal sphincter to lower resting anal pressure. Simple removal of the hemorrhoidal mass is not enough in individuals who have hemorrhoids and constipation; the resting anal pressure must be lowered either by sphincterotomy or dilatation. The fact was substantiated that our one thousand cryohemorrhoidectomized patients without sphincterotomy presented high incidence of recurrences (21) as opposed to present studies.

Despite the general fear of incontinence following internal sphincterotomy, our results show a very low and usually temporary incidence which does not seriously incapacitate social activity. We believe that lateral internal sphincterotomy for anal ulcer is the most secure and reliable modality of treatment to date, and encourage adoption of this technique.

TABLE II

Results of Internal Sphincterotomy

REFERENCE	NO. OF PATIENTS	HOSPITAL STAY	HEALING TIME (weeks)	CURE RATE (%)	MINOR DEFECT (%)
Hawley ('69)	24	5	3.5	100.0	0.0
Notaras ('69)	66	—	3	100.0	6.0
Hoffman & Goligher ('70)	99	Ambulatory	4	97.0	12.0
Notaras ('71)	73	—	3	100.0	10.0
Miller ('71)	99	Ambulatory	2	100.0	3.0
Ray et al ('74)	21	1st bowel movement	4	100.0	5.0
Rudd ('75)	200	Ambulatory	2	99.5	0.5
Nwako ('75)	22	4	1.5	95.5	4.5
Bailey et al ('78)	418	—	6	93.3	2.2
Abcarian ('80)	150	2	3	99.7	0
Oh (Present)	750	3	3*	97.6	2.4

* Limited to anal ulcer

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Acute Intraabdominal Hemorrhage from Ruptured Aneurysms of the Splenic Artery

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Abstract

Aneurysms of the splenic artery are rare and are often asymptomatic. Their precise pathogenesis and natural history are as yet incompletely understood. Rupture of a splenic artery aneurysm is unpredictable and life threatening with an overall mortality of about 25 percent. Two cases of ruptured splenic artery aneurysms are presented. In each, rupture was the initial presentation of the aneurysm and each was successfully operated upon. Rupture of a splenic artery aneurysm should be considered in all cases of acute intraabdominal hemorrhage of uncertain etiology.

Aneurysms of the splenic artery are rare with an incidence in the general population estimated at 0.07 percent (1). Until recently only 900 cases were documented in the world literature (2). Their etiology and clinical significance are as yet incompletely understood. There seems to be a predilection for females, especially multiparous women having had six or more pregnancies. Splenic artery aneurysms are also more commonly seen in patients with spenomegaly secondary to portal hypertension and following contiguous inflammatory processes such as pancreatitis. Rupture of a splenic artery aneurysm is unpredictable and life threatening with an overall mortality after rupture of about 25 percent (1). This mortality climbs to 75 percent when rupture occurs during pregnancy (5). This report presents two older patients seen at the City Hospital Center at Elmhurst who were successfully operated upon for ruptured splenic artery aneurysms.

Case Report

Patient #1:

A sixty-two-year old Caucasian woman was brought to the emergency room after fainting. She had just walked up six flights of stairs and suddenly became dizzy and lost consciousness for an unknown length of time. The past history was remarkable for a cardiac arrythmia for which the patient had been taking Digoxin and for some unknown thyroid surgery many years previously. The patient had never been pregnant.

Although alert on admission, her systolic blood pressure was 70mmHg with antishock trousers in place. Her examination was only remarkable for a prominent aortic pulse in the epigastrium. A nasogastric tube was passed and clear bile was aspirated from the stomach. The hematocrit on admission was 31 volume percent and dropped to 25 volume percent during resuscitation with crystalloid solutions. A chest x-ray was normal. A flat plate of the abdomen showed a medial shift of the gastric bubble and no abnormal calcifications. An EKG showed sinus tachycardia without ectopic beats.

The patient was taken immediately to the operating room for laparotomy. Several hundred milliliters of blood were free in the peritoneal cavity. There was a hematoma in the splenic hilum which appeared to extend into the transverse mesocolon. The spleen itself was normal as were the rest of the abdominal viscera and aorta. After gaining control of the splenic artery near its origin, a splenectomy was performed. Examination of the excised specimen revealed a ruptured splenic artery aneurysm. The aneurysm, which

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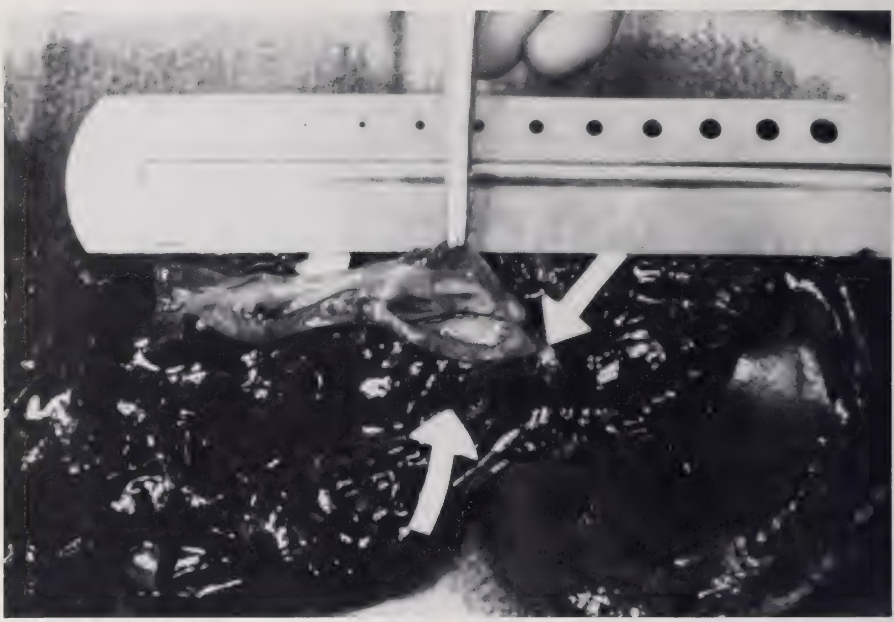

FIG. 1. Excised specimen showing a saccular aneurysm (pointer) with surrounding hematoma (arrows) of one of three splenic artery branches near the hilum.

arose from one of the three branches of the artery near the hilum, was saccular in shape and measured 2.5 × 2.5 centimeters (Fig. 1). Histologic sections taken from the region of the aneurysmal dilitation showed total degeneration of the elastica interna and externa with replacement of the media by thin fibrous tissue (Fig. 2). Postoperatively, the patient recovered uneventfully and was discharged from the hospital in eleven days.

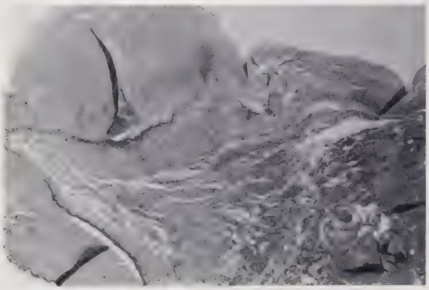

FIG. 2. Histologic section taken from the aneurysm shown in Fig. 1. There is degeneration of the medial coat, discontinuation of the elastica interna and externa, nodular thickening of the intima, and replacement of the wall further on by fibrous tissue (upper right) where the rupture occurred. (Elastica Van Gieson Stain, 16×).

Patient #2:

A fifty-four-year old Greek woman, hypertensive on no medications, with known postnecrotic cirrhosis, came to the emergency room complaining of four days of epigastric pain. On the day of admission, the pain became worse and she developed left shoulder pain. On examination, she was found to have orthostatic hypotension and diffuse abdominal tenderness with shifting dullness. Clear bile was aspirated from the stomach. The hematocrit was 20 volume percent and the platelet count 52,000/mm^3. She was admitted to hospital and transfused with five units of blood. Fresh frozen plasma and vitamin K were also given. A paracentesis produced bloody ascitic fluid. An emergency arteriogram showed an aneurysm of the distal splenic artery (Fig. 3) and evidence of portal hypertension.

At laparotomy bloody ascitic fluid was noted. The spleen was enlarged and the liver cirrhotic. It appeared that the aneurysm had leaked and then

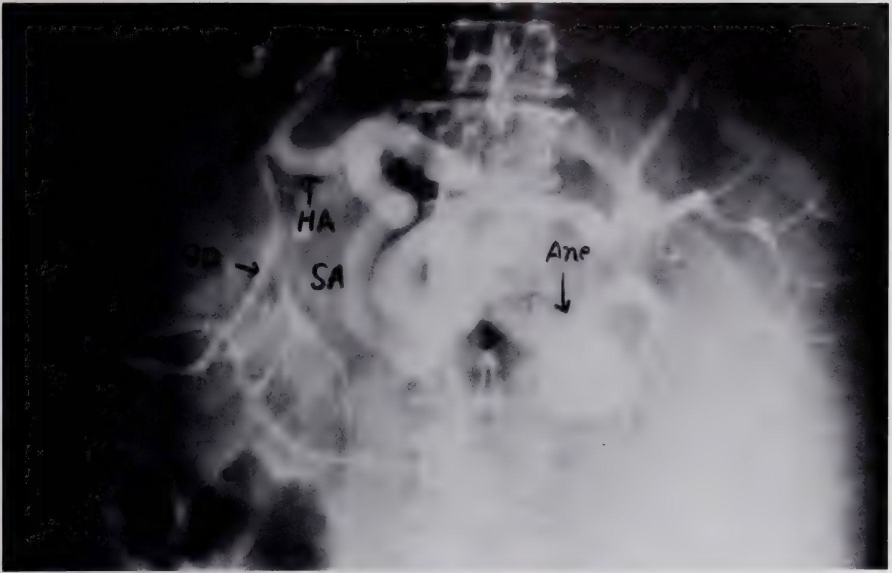

FIG. 3. Celiac angiogram from patient MN showing the saccular aneurysm (ANE) of the distal splenic artery. SA-Splenic Artery, HA-Hepatic Artery, LG-Left Gastric Artery, GD-Gastroduodenal Artery.

sealed off. An aneurysmectomy, splenectomy and liver biopsy were performed. Examination of the excised specimen showed the aneurysm to be 3.0 centimeters in diameter (Fig. 4). Histologic sections of the splenic artery near the aneurysm showed replacement of the media by thin fibrous tissue.

Postoperatively, the patient developed a mild coagulopathy which was corrected with infusions of fresh frozen plasma. She also ran low grade fevers without a clear source but which resolved with broad spectrum antibiotics. She was discharged from the hospital on the twenty-second postoperative day.

Discussion

Although uncommon, splenic artery aneurysms comprise about 58 percent of all visceral artery aneurysm (1). They were first described by Beaussier in 1770 (3). Aneurysms of the splenic artery are often asymptomatic but may cause left upper abdominal or left scapular pain especially when acutely expanding. In one series of 68 patients reported by Stanley and Fry (4), 5.3 percent had ruptured at the time of diagnosis.

The precise pathogenesis of these lesions is yet to be defined. They are usually saccular in shape. Fibromuscular dysplasia and medial degeneration of the artery wall are common findings. Calcification of the wall of the aneurysm is thought to be a secondary event (4) and a curvilinear calcification in the left upper quadrant on plain abdominal film may be the first indication that an aneurysm is present. Splenomegaly is also a frequent finding and an increased volume and velocity of blood flow in the splenic artery secondary to this is felt to play a role in the formation of the aneurysm (4). This may be a major factor in the formation of splenic artery aneurysms in patients with portal hypertension.

There appears to be a higher incidence of splenic artery aneurysms in women, especially those completing six or more pregnancies (1, 3–5). The gestational factors leading to aneurysm formation are still incompletely understood. Hormonally induced changes in elastic tissue and in medial ground substance of arteries normally occurs during pregnancy and usually reverts to normal following delivery. It may be that repeated pregnancies cause irreversible changes in the wall of the splenic artery and ultimately lead to aneurysm formation (1, 4). Increased splenic artery blood flow secondary to the

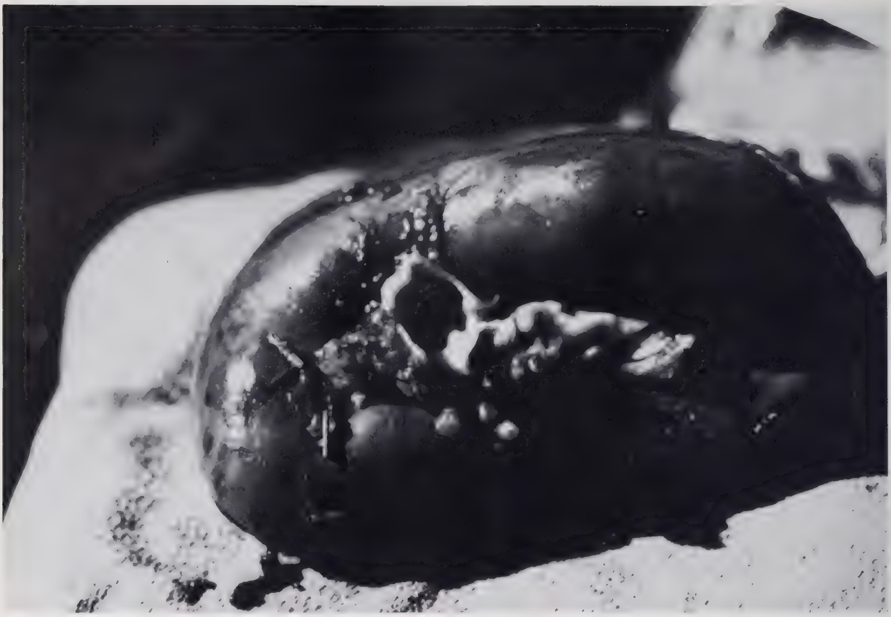

FIG. 4. Excised spleen along with the saccular splenic artery aneurysm seen in Fig. 3.

splenic arteriovenous shunting which normally occurs during pregnancy may also play a role.

The management of patients with asymptomatic splenic artery aneurysms remains unclear. In young women of child bearing age resection is probably indicated due to the increased hazard of rupture during pregnancy (1, 4, 5). Rupture of a splenic artery aneurysm during pregnancy usually occurs during the third trimester and carries a 75 percent maternal and a 95 percent fetal mortality (5). The management of aneurysms discovered in older asymptomatic patients is more problematic. Stanley et al (1) feel that splenic artery aneurysms in all patients should be resected if they are otherwise good surgical risks. Their view stems from an estimated overall incidence of aneurysm rupture of 8 percent with a mortality of 25 percent once rupture has occurred. Busuttil and Brin (5) advise a more conservative approach in older asymptomatic patients with aneurysms less than two centimeters in diameter.

Since a majority of splenic artery aneurysms occur close to the splenic hilum where the artery divides, splenectomy is usually required when resecting the aneurysm. In those cases in which the aneurysm is at some distance from the hilum, simple ligation of the aneurysm or aneurysmectomy with preservation of the spleen may be possible. When acute rupture has occurred, splenectomy is probably the most expeditious approach. In poor risk patients with symptomatic aneurysms, transcatheter arterial embolization of the aneurysm with stainless steel coils under local anesthesia inducing thrombosis of the aneurysm may be an alternative approach (6).

Summary

The two case reports presented here illustrate two ways in which these uncommon aneurysms may present. In both cases acute rupture was the initial presentation of the aneurysm. In the first case (BC) no specific risk factor for aneurysm formation was identified. Portal hypertension may have contributed to the formation of the splenic artery aneurysm in the second case (MN). It seems clear that rupture of a splenic artery aneurysm should be considered in all cases of

acute intraabdominal hemorrhage of uncertain etiology.

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Maxillary Sinusitis: Isolation of *Scedosporium (Monosporium) apiospermum,* Anamorph of *Petriellidium (Allescheria) boydii*

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Abstract

Infections of the paranasal sinuses with fungi are rare. The affected individuals are usually immunodeficient, having been compromised by corticosteroids, cytotoxic drugs, or debilitating diseases. This report involves a patient with long-standing sinusitis, which was colonized by *Scedosporium (Monosporium) apiospermum.* The organism is the imperfect state or anamorph of *Petriellidium (Allescheria) boydii.* The fungus was found in the antral lavage. The patient made a rapid recovery following an intranasal antrostomy, which provided aeration and drainage. Specific antifungal chemotherapy was not required.

Case Report

The patient was a 57-year-old woman who had been in poor health for a number of years. Her past history included right maxillary sinusitis following an infection of the first molar tooth twelve years previously, partial gastrectomy for bleeding peptic ulcer, adrenocortical insufficiency, hypothyroidism, and heavy cigarette smoking. She suffered frequent migraine headaches for which she had been treated with methysergide.

In 1978, endocarditis and pleuritis developed, complicated by meningitis and brain abscess. She was treated for many months with penicillin. No microorganism was isolated as the etiologic agent.

In 1979, headaches recurred with increased frequency and severity. Computerized tomography revealed opacification of the right maxillary sinus. Radiographic examination revealed marked clouding of the maxillary sinus, and mild clouding of the frontal sinus and ethmoids on the right side. The left side was clear. Irrigation of the right antrum yielded fluid mucopus with clumps of greyish exudate, suggesting a fungal infection. The microbiology laboratory reported *Klebsiella oxytoca,* and a fungus, isolated at the same time. A subculture of the latter was sent to the mycology laboratory of the New York City Department of Health, where it was identified as *Scedosporium (Monosporium) apiospermum.*

The patient was treated for two weeks with cephalexin for the *Klebsiella* infection, without improvement. An intranasal antrostomy was performed, because of continued headache and nasal discharge. There was immediate relief, and the patient recovered. As hyphae were not demonstrated in the mucosa on histopathologic examination, antifungal chemotherapy was not required.

Discussion

The first instance of human infection with *Scedosporium (Monosporium) apiospermum* was reported by Radaeli in a case of Madura foot in a Sardinian farmer in 1911 (1). The fungus is the most frequent organism isolated from mycetoma in Europe and the Americas; it also infects other tissues. It is commonly found in the soil (2).

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The isolate described in this report, *S.* (*Monosporium*) *apiospermum,* is the asexual or anamorphic state of *Petriellidium* (*Allescheria*) *boydii.* These two fungi were accepted as different agents of mycetoma until Emmons in 1944 (2) showed that *Scedosporium* (*Monosporium*) was actually the imperfect (asexual) stage of what was then known as *Allescheria boydii.* Both *Scedosporium* and *Petriellidium* grow rapidly on common laboratory media, producing a light grey fluffy colony, becoming smoky grey with age. The conidia are pale brown, ovate or clavate and are born singly or in small groups laterally and at the tips of simple or branched conidiophores. The sexual or telemorphic state is distinguished from the asexual state in that the former produces a globose, nonostiolate, light brown to black, membranaceous cleistothecia containing asci and ascospores. The ascospores are ovoid to ellipsoidal, pale yellow-brown, and smooth-walled (2).

Review of Recent Cases

Three cases of maxillary sinusitis caused by *P. boydii* have been reported in recent years.

In 1977 Gluckman et al (3) described the first case of orbital invasion by the fungus in a 58-year-old man who suffered from diabetes, Laennec's cirrhosis, and renal failure. The clinical presentation resembled that of mucormycosis. Amphotericin B was administered and a Caldwell-Luc operation was performed. He died three months later from the underlying diseases.

Hecht and Montgomerie reported a case in 1978 (4). Their patient was a 20-year-old man with acute lymphoblastic leukemia. Amphotericin B was used unsuccessfully. He died one month after admission. *In vitro* susceptibility of the fungus to miconazole was reported after his death.

Bark et al, also in 1978 (5) reported a 28-year-old diabetic woman with a history of pain over the right antrum radiating to the ear. She was treated with sinus irrigations and antibiotics without relief. A Caldwell-Luc operation was performed two months later. Microbiologic cultures grew *Klebsiella pneumoniae, Enterobacter cloacae* and *P. boydii.* The patient recovered without additional therapy.

Two cases of *sphenoidal* sinusitis due to *P. boydii* have also been described in the recent literature.

Mader et al in 1978 (6) reported a 33-year-old woman who suffered from severe right frontoparietal headaches with occipital radiation for three months. She had experienced recurrent rhinorrhea for six years. Past history was negative for diabetes, surgery, trauma, immunosuppressive agents, and foreign travel. Radiographs revealed a soft tissue mass in the sphenoid sinus and destruction of the floor of the sella turcica. Transeptal sphenoidotomy was performed with drainage of purulent exudate. Histologic examination revealed branching septate hyphae in the mass, but not in the underlying mucosa or bone. *Citrobacter fruendii* and *P. boydii* were cultured. She was treated with miconazole and recovered. The fungus was resistant *in vitro* to amphotericin B.

Bryan et al in 1980 (7) reported a 47-year-old woman with intracranial involvement who died despite surgical drainage and intensive therapy with miconazole. These investigators employed direct fluorescent antibody staining and immunodiffusion serologic tests in addition to successful culture for specific identification of the organism.

The foregoing cases demonstrate the importance of early isolation of the fungus, and prompt surgical intervention to forestall spread of the invasion to surrounding tissues.

Current Antifungal Chemotherapy

Mohr and Muchmore (8) reported that *P.* (*A.*) *boydii* is not susceptible to amphotericin B within the range of human tolerance.

Lutwick et al (9) reported three patients with deep infections of the limbs due to *P. boydii,* who were treated effectively with miconazole. One patient also had concomitant surgery.

Speller (10) reviewed the various classes of antifungal agents and reported that miconazole was active in the treatment of *Petriellidium* infections. The fungus was also inhibited *in vitro* by oestradiol, which was used successfully in one case of mycetoma.

Borgers (11) stated that the imidazole derivatives inhibit the biosynthesis of ergosterol, the main sterol in cell membranes of fungi. These agents also affect the synthesis of triglycerides and phospholipids. Changes in oxidative and peroxidative enzyme activities which lead to an intracellular build-up of toxic concentrations of peroxide may contribute to the observed deterioration of subcellular organelles and to cell necrosis.

Drouhet and Dupont (12) reported favorable results with ketoconazole in the treatment of various mycoses; four patients with infection due to *P. boydii* improved. The drug was given orally in doses of 400 mg per day. Measurements of ketoconazole in the serum during treatment were useful in the evaluation of therapy. Treatment may be required for two to nine months.

Symoens et al (13) reported results of treatment with ketoconazole of 1104 patients in Europe and the Americas with superficial and deep mycoses. There were five patients with mycetoma caused by fungi. There was marked improvement in one patient with infection due to *P. boydii* after eight months of treatment. Ketoconazole was given orally and was well tolerated. No abnormalities in hematologic or biochemical indices were noted.

Summary

We are reporting a case of colonization of the maxillary sinus by *Scedosporium* (*Monosporium*) *apiospermum*. The fungus is the anamorph of *Petriellidium* (*Allescheria*) *boydii*. The patient's resistance had been compromised by months of treatment with antibiotics for endocarditis and meningitis, and corticosteroids for adrenocortical insufficiency. Conservative intranasal antrostomy for aeration and drainage of the sinus was followed by rapid recovery. Specific antifungal chemotherapy was not required.

The first cases of sinusitis due to this fungus, and its antifungal chemotherapy were reviewed.

Acknowledgments

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Diffuse and Transient Gyral Enhancement on CT Following Seizures in Crohn's Disease

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Abstract

A twenty-one-year-old woman with Crohn's disease had diffuse and bilateral gyral enhancement on postcontrast CT scan of the head, six hours after the onset of seven Grand Mal seizures. A follow-up CT scan ten days later showed no abnormality. Although transient gyral enhancement has previously been described in cerebrovascular disease, meningoencephalitis, and focal seizures, this has been reported neither in generalized seizures nor Crohn's disease. Possible underlying pathologic mechanisms producing this condition are discussed.

Selective focal gyral enhancement in Computerized Tomography (CT) scans, following intravenous administration of iodinated contrast media is a well known finding in patients with cerebral ischemia or infarction and less frequently with meningoencephalitis. Kinkel et al (1) described this abnormality in patients with transient ischemic attack without any other parenchymal changes. They believe that the gray matter enhancement due to vascular dysautoregulation with secondary reactive hyperemia and breakdown of the blood brain barrier represents the first sign of cerebral hypoxia in CT scans. Included in their report was a case of gray matter enhancement in a patient with focal seizures caused by hypotension during recovery from general anesthesia for surgery. CT scan performed twenty-four hours after the onset of the seizures showed only postcontrast focal gyral enhancement (1, 2). Zimmerman et al (3) reported a case of focal seizures in a four-year-old boy, eight days after the onset of meningitis. His CT scan showed bilateral parietal gyral enhancement. Rumack et al (4) published a case of a two-year-old boy with an abnormal CT scan obtained two hours after the onset of right focal seizures. An oval area of low density located medial to the left occipital horn was noted to be enhanced centrally following administration of contrast media. Follow-up CT scans two weeks and one month later, respectively, were normal.

Case Report

A twenty-one year old female student with an eleven year history of Crohn's disease was admitted to The Mount Sinai Medical Center on July 14, 1980 with abdominal pain, cramps and diarrhea. Although her father has an idiopathic seizure disorder, she had no past history for seizures. She had been on prednisone and codeine prior to the admission. A general physical examination was negative except for diffuse abdominal tenderness.

Laboratory tests were all within normal limits, other than minimally low chloride (91 mEq/L) and sodium (133 mEq/L), and minimally high alkaline phosphatase (97 M.U./ML). On July 15, 1980 she underwent a sigmoidoscopy. On the following day, she had a sudden onset of seven Grand Mal seizures in a period of three hours, that involved both sides of the body except for the last one which was of right focal onset.

Neurologic examination revealed a stuporous patient in postictal state reacting only to noxious

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stimuli, mainly on the right side. Oculocephalic maneuvers showed that her eye moved better towards the right. The remaining neurologic examination was unremarkable. She was treated with phenobarbital and diphenyl-hydantoin. The precontrast CT scan of the head six hours after the onset of the seizures demonstrated no significant abnormalities, whereas the postcontrast study with intravenous drip of 150 cc of 60% Iothalamate Meglumine showed marked gyral enhancement of the frontal, parietal and occipital lobes, most marked in the parietooccipital areas bilaterally (Fig. 1A–1D). An Isotope brain scan was normal.

A lumbar puncture yielded no abnormality including pressure, chemistry, cytology and culture. There was no laboratory evidence of coagulopathy. On the following day she became responsive and alert. Progressive abdominal distension was, however, noted. On July 22, 1980 a decompression was performed for a colonic obstruction secondary to Crohn's disease. Follow-up pre- and postcontrast CT scans of the head ten days later were normal. Although she experienced three more grand mal seizures on August 2, 1980, one day after a subtotal colectomy and end ileostomy, her postoperative recovery was otherwise uneventful. She was discharged on August 15, 1980 on phenobarbital, diphenlhydantoin and prednisone. She has been free of seizures ever since (16 months).

Discussion

The etiology of seizures in this case is not clear. The family history of epilepsy, slight electrolyte abnormalities on admission and a prolonged treatment with codeine and steroids, could all be contributing factors. Systemic arterial and venous thromboembolytic complications do occur frequently in ulcerative colitis; however, they rarely involve the cerebral vessels. Mayeaux and Fahn (5) reported three such cases. Hypercoagulability associated with chronic ulcerative colitis (6) and Crohn's disease (7) has also been reported. However, no laboratory evidence of coagulopathy was found in our patient.

Cerebral arteritis should also be considered as a cause of seizures. Hemorrhagic complications (intracerebral hematoma) due to arteritis was reported by Edward (8) in one patient with ulcerative colitis. Although headache and seizures with or without abnormalities in the peripheral blood or CSF may be the predominant features, neurologic deficits are usually more prominent and severe in these cases. No headache or hemorrhage was noted in our patient. Indeed, she had such a benign course that no cerebral angiography was performed. Embolization causing seizure is not likely because of her normal cardiac status and a rather extensive enhancement without objective neurologic deficits. Her age also precludes a possibility of occlusive disease secondary to arteriosclerosis.

The exact etiology of the pathophysiology that occurs in the central nervous system during seizures is not known. Several theories have been postulated. First, the blood brain barrier (B.B.B.) is a highly sophisticated filter mechanism which limits blood borne solutes transversing it (11). Alterations of the B.B.B. to plasma proteins have been described in drug-induced seizures (10). It was found that the intracerebral penetration of albumin I^{-125} was increased in laboratory animals that were artificially seizure induced and its degree was directly proportional to the duration of the seizures. This phenomenon did not appear to be dependant upon blood flow or vasodilation but rather upon enhanced vascular permeability (E.V.P.). This alteration E.V.P. was reversible. Thus increased penetration of plasma proteins into the C.N.S. during experimentally induced seizures has been reported to be a result of reversible altered cerebrovascular permeability (10).

Secondly, in humans it has been established that increased neuronal metabolism can induce a rise in regional blood flow (R.B.F.) during active seizures (12). It has also been shown that cerebral blood flow (C.B.F.) increased two to ten times in epileptic foci (17). Thus, increases in C.B.F. and R.B.F. could be explained in part by regional metabolic changes in the cerebral cortex during seizure activity (19–21). The increased blood flow can be detected as early prominent cerebral veins on angiography in patients with focal seizures (13, 18). This effect was reversible when seizure activity subsided. Thirdly, transient C.T. changes are rarely seen and have been reported only following focal seizures (11, 13, 15). Our case is unusual because diffuse rather than focal gyral enhancement following prolonged generalized seizures.

Conclusion

Our impression is that gray matter enhancement should, however, be considered as a possible finding after repetitive seizures. This most likely represents a reversible benign abnormality caused by alterations in the B.B.B. cerebral metabolic rate and possible in cerebral blood flow perfusion.

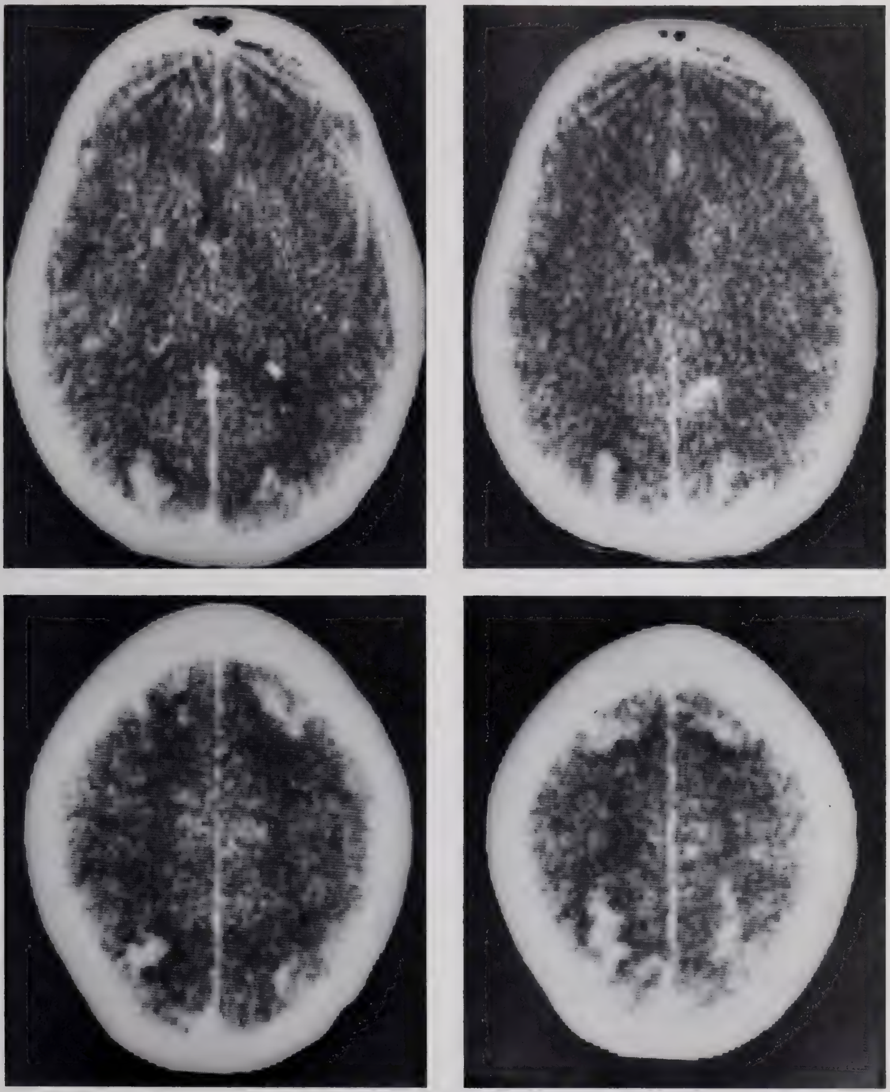

FIG. 1. Postcontrast CT scans of the head. Multiple CT sections in exaggerated inferior orbitomeatal plane at four different levels from the atrium to the vertex (Fig. 1A, B, C, D) show multiple focal enhanced areas on both sides of the hemispheres, particularly posteriorly. No ventricular deformities or shift was noted.

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Hypernephroma Metastatic to a Parathyroid Adenoma Eighteen Years after Nephrectomy

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Abstract

The hitherto unreported observation of a deposit of metastatic renal cell carcinoma (hypernephroma) in a surgically removed parathyroid adenoma is documented. Nephrectomy had been performed 18 years previously with no evidence of recurrent tumor in the interim. The unusual behavior of hypernephroma as regards the potential for delay in metastasis and peculiar sites of secondary spread are briefly referred to.

Introduction

The biologic vagaries of renal cell carcinoma (hypernephroma) represent the most fascinating aspect of this neoplasm. Among these is the occasional extended latent period before metastatic disease becomes clinically manifest. Reports of intervals in excess of 30 years between nephrectomy and metastasis have been recorded (3, 4, 7). One report documents death from pulmonary metastases 50 years after nephrectomy (8). Unusual sites of metastasis have been observed in hypernephroma. These include such locations as the gallbladder, bile ducts, appendix, eyelid, breast, umbilicus, meninges and atrioventricular node (1). We report the observation of metastatic hypernephroma in a functioning parathyroid adenoma for which the patient underwent neck exploration. To our knowledge, this is a previously unrecorded finding.

Case Report

The patient is a 79-year-old woman with hypertension of 35-years duration and mild diabetes mellitus controlled by diet. In 1963, after an episode of painless hematuria, intravenous pyelography and aortography disclosed the presence of a hypernephroma and a left nephrectomy was performed at another institution. There was no clinical evidence of extrarenal spread at surgery or of metastatic disease in the ensuing eighteen years.

In February 1979, she was readmitted for evaluation of deteriorating mental status, confusion, poor coordination and abnormal reflexes. A diagnosis of organic mental syndrome was made. Computerized axial tomography (CAT) scan and cerebral angiography revealed a 5 × 6 cm mass in the right middle fossa consistent in appearance with a sphenoid ridge meningioma. An elevated serum calcium of 13.6 mg/dl was noted. Serum parathormone was 147 pg./ml (upper limit of normal 100 pg./ml). Serum calcium levels were reduced by lasix and intravenous saline. Exploration of the neck for hyperparathyroidism as well as brain surgery were deferred because of the patient's poor general condition.

In January 1980, the patient fell in the bathtub and was readmitted to the hospital. CAT brain scan showed no change. Serum calcium was 12.5 mg/dl.

One year later, she was again admitted because of lethargy, confusion, mild left hemiparesis and intermittent urinary incontinence. Serum calcium was 12.1 mg/dl and serum phosphorus 2.2 mg/dl. A repeat CAT brain scan again showed no change from previous studies.

It was felt that hyperparathyroidism might, in

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part, be responsible for her deterioration and neck exploration was undertaken. An enlarged right upper parathyroid gland was removed. A normal right lower parathyroid gland was identified and left in place. The left thyroid lobe was involved by a large nodular goiter which was not disturbed. The left parathyroid glands were not identified. Postoperatively, serum calcium levels remained in the 8.3–8.6 mg/dl range until discharge on the 12th postoperative day. Although her mental state became clearer, neurologic deficits remained unchanged.

Re-evaluation of the right cerebral mass, following report of the pathologic findings, included the possibility of metastatic hypernephroma. Since the patient remained a poor risk for brain surgery, cranial radiotherapy was instituted.

Pathologic Findings

An enlarged parathyroid gland measuring 1.6 cm in diameter and weighing 3.3 g was received for frozen section diagnosis. The sample selected for cryostat section showed a diffuse proliferation of small to medium-sized chief cells in solid trabecular and microacinar pattern. No significant fat was present. The frozen section diagnosis was "enlarged parathyroid, consistent with adenoma or hyperplasia." The surgical exploration yielded no other enlarged glands and no further tissue was removed. The entire specimen was fixed routinely in 10% formalin and completely sectioned and embedded for histologic study. Sections were stained with hematoxylin and eosin as well as periodic acid-Schiff reaction, with and without diastase pretreatment.

The histologic findings on permanent paraffin section confirmed the frozen section impression of a diffuse chief cell proliferation. There were small, scattered foci of oxyphils and the chief cells showed minimal nuclear pleomorphism with no mitotic activity. In some sections, a delicate limiting fibrous capsule could be seen with externally located remnants of nonneoplastic parathyroid elements (Fig. 1). One section included a small nodular focus comprising cells of a totally different character, not present in the frozen section block. This element was approximately 0.2 cm in diameter, occupying a very small fraction of the adenomatous gland. It consisted of generally uniform large clear cells with abundant cytoplasm and a relatively small central or eccentric ovoid nucleus. Cell borders were sharply defined and there was a prominent, highly vascular stroma with dilated and engorged thin-walled vessels. Evidence of recent and old hemorrhage (hemosiderin deposits) were noted in the nodule which was located near the periphery of the adenoma (Figs. 2 and 3). The PAS and diastase-PAS stains revealed an abundance of glycogen in the clear cytoplasm of the constituent cells of the nodule. These features were characteristic of clear cell carcinoma of renal origin, an impression which

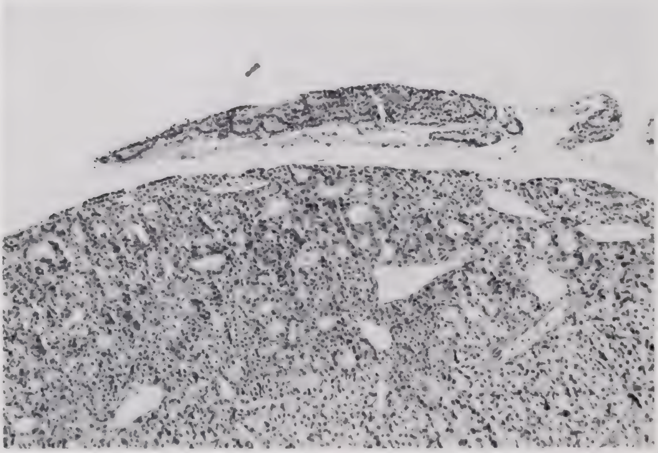

FIG. 1. Periphery of parathyroid adenoma showing small chief cell component, delicate capsule and extracapsular glandular elements (hematoxylin and eosin ×100).

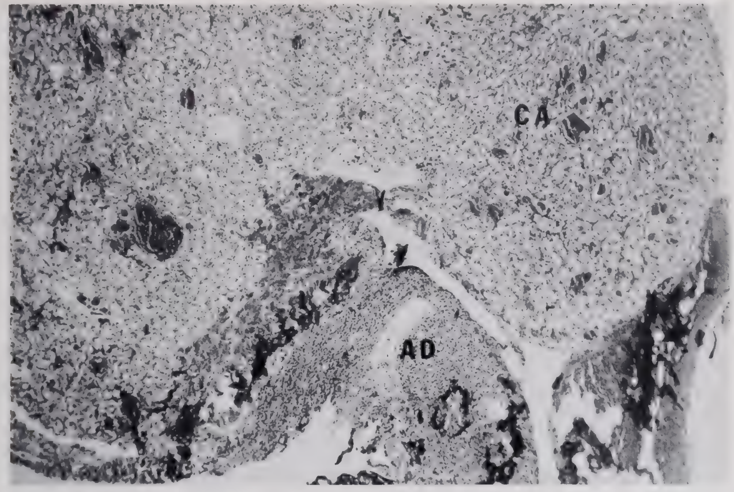

FIG. 2. Low magnification of a major portion of nodule of metastatic renal cell carcinoma (CA) in parathyroid adenoma (AD) (hematoxylin and eosin ×40).

was supported by the information that a nephrectomy had been performed 18 years previously. The original pathology report and histologic sections were obtained (through the courtesy of Dr. Leopold Reiner, Director of Laboratories at Bronx-Lebanon Hospital Center). Review of this material indicated that a 6.0 cm hypernephroma involving the left kidney was excised in 1963, the tumor comprising clear cell elements identical with those of the metastatic nodule in the parathyroid adenoma (Fig. 4). The renal vein was free of tumor in the nephrectomy specimen.

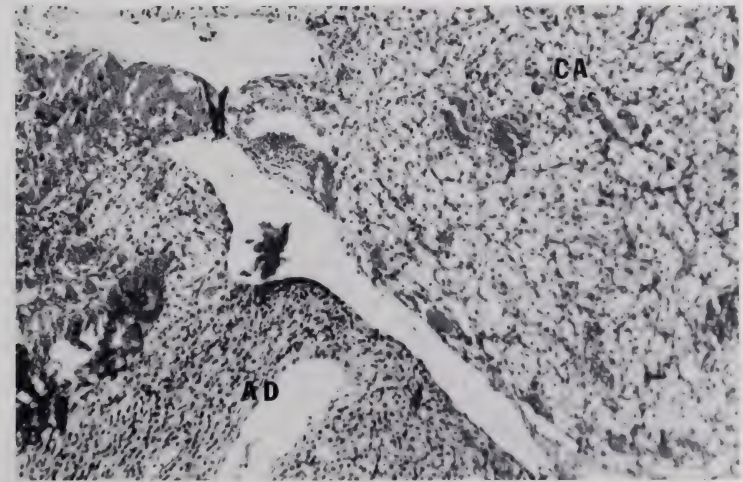

FIG. 3. Interface of chief cell adenoma (AD) (lower left) and metastatic clear cell carcinoma (CA) at higher magnification (hematoxylin and eosin ×100).

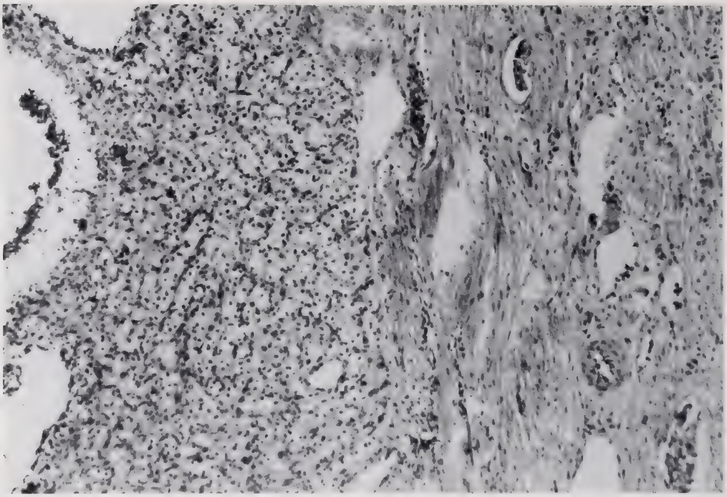

FIG. 4. Renal cell carcinoma (clear cell type) including portion of uninvolved parenchyma, from nephrectomy specimen 18 years prior to parathyroidectomy (hematoxylin and eosin ×100).

Discussion

A single reference to metastatic renal cell carcinoma involving the parathyroid has been found in our review of the literature (2). A prospective postmortem study of parathyroid glands in 160 consecutive patients dying with a variety of malignant tumors revealed metastatic involvement of at least one gland in 12%. This compared to an incidence of 5.3% in 750 autopsies, retrospectively reviewed by the same investigators. The most common primary tumor sites were the breast, blood (leukemia), skin (melanoma), lung, soft tissue (sarcomas) and lymph nodes (lymphoma). One case in the prospectively analyzed autopsy series represented hypernephroma. The kidney was not the primary tumor site in any of the 40 retrospectively studied cases with parathyroid metastases. Another postmortem study (6) which was aimed at the detection of metastatic involvement of endocrine glands, revealed only three cases with parathyroid metastases in 1,900 patients with malignant disease (0.2%), representing single cases of thyroid and laryngeal carcinoma and one with Hodgkin's disease.

We are able to cite two case reports of metastatic carcinoma in parathyroid adenomas, both primary breast cancers (5, 9). The patient reported by Woolner et al (9) was a 54-year-old woman with evidence of nephrocalcinosis nine years prior to mastectomy. A 7.5 g parathyroid adenoma was excised one year after removal of her breast because of persistent hypercalcemia, hypophosphatemia, elevated serum alkaline phosphatase, increasing azotemia and skeletal lesions suggesting hyperparathyroidism. The parathyroid adenoma contained a deposit of metastatic cancer comprising approximately one-third of the tumor. The serum calcium returned to normal levels postoperatively.

Our patient apparently represents the first recorded instance of renal cell carcinoma metastatic to a symptomatic parathyroid adenoma, the secondary deposit being a fortuitous finding during histologic study of the surgically resected gland. One may speculate that the parathyroid parenchyma, being highly vascular, served as a "fertile soil" for circulating tumor cells. However, this fails to account for the clinical dormancy of 18 years. The biological behavior of renal cell carcinoma remains enigmatic and unpredictable, presenting unexpected challenges to both the clinician and pathologist.

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Salmonellosis and Ruptured Abdominal Aortic Aneurysm: A Case Report

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Infection of the aorta is rare (1). This resistance to infection may be compromised in the presence of vascular anomalies such as patent ductus, coarction, arteriovenous malformations and other arterial lesions like atherosclerosis, idiopathic cystic medial necrosis, coronary arteritis and syphilitic arteritis (2). Enteric pathogens including members of the Salmonella group may invade such abnormal vessels (3). The majority of infections involving larger vessels are found in areas of arteriosclerotic change with aneurysmal rupture as a common outcome. In most cases the infections have occurred in elderly debilitated patients with the diagnosis made during surgery or at autopsy.

Infected aneurysms of the aorta were found in 2.6% of 338 abdominal aneurysms studied at the Boston City Hospital in 1960 (4). Salmonella is becoming more frequently implicated in seeding the aorta. Mundth et al (5) at the Massachusetts General Hospital reported that Salmonellosis comprised 33% of the infected aneurysms studied while Staphylococcus aureus and E. coli accounted for 25% and 17% respectively.

Mendelowitz et al (6) studied the twenty-five known cases (up to 1979) of abdominal aortic salmonellosis; only six of these patients survived. Because it is so lethal, early recognition of this entity is important. This report describes a case of impending ruptured aortic aneurysm associated with salmonellosis, reviews the pathogenesis, clinical presentations, diagnosis and treatment of the disease.

Case Report

A 69-year-old man was readmitted to Saint Barnabas Medical Center for persistent lower back pain which radiated to the groins, left lower quadrant pain, anorexia and weight loss. He had previously been admitted six weeks earlier for pneumonitis and Salmonella septicemia. At that time, he presented with dyspnea, diarrhea, lower back and abdominal pain associated with fever and chills. After two weeks of antibiotic treatment, his course improved. The aforementioned symptoms resolved except a persistent lower back pain which was believed to be due to his past history of chronic lumbosaccral arthritis. His other past medical history included chronic obstructive lung disease, artherosclerotic heart disease, left bundle branch block, macrocytic anemia but without myocardial infarction. His past surgical history included subtotal gastrectomy for gastric ulcer, inguinal hernia repair, and hemorridectomy.

Physical Examination: Body temperature 100.4 F, pulse rate 60, respirations 20 and blood pressure 144/88. Cardiac examination was remarkable for cardiomegaly with displaced apex beat to the sixth intercostal space. Pulmonary examination was remarkable with decreased breadth sound at the left base and diffuse rhonchi over the entire lung field. The abdomen was soft with no masses or organomegaly. The patient had tenderness on palpation of the left lower quadrant without any visible pulsations. Normal bowel sounds were heard. There were no Grey Turner's sign or Cullen's sign. Femoral pulses were 1+ bilaterally with no pulses palpable distally.

Laboratory Data: Hemoglobin 10.2 gm/100 cc, hematocrit 30.4, WBC 18,100/cu mm with 84% polymorphonuclear leukocytes, 9% band forms, 5% lymphocytes and 1% monocytes. ESR 64. SMA 6/12 channels were unremarkable except for BUN 34 and alkaline phosphatase 316.

A chest roentgenogram revealed cardiomegaly, discoid atelectasis at left base but without active pulmonary parenchymal disease. Blood culture was positive for Staphylococcus epidermidis. A

This work was completed during Mr. Kwai's third year of medical school at Mount Sinai.

series of liver scan, bone scan, test for occult blood, urine culture, gastroscopy and ultrasound were ordered to rule out metastatic carcinoma. Ultrasound reported a distended gallbladder with no definite opacities within. A retroperitoneal mass with pulsation consistent with abdominal aortic aneurysm which had an anterior-posterior diameter of 4.5 cm was noted. Based on clinical grounds and the ultrasound report, a diagnosis of impending ruptured abdominal aortic aneurysm was suspected. The patient was immediately taken to emergency surgery.

Surgery was carried out through a midline incision extending from xiphoid to pubic symphysis. Exploration of the abdominal cavity revealed a large pulsating mass located at the retroperitoneal area with some bluish appearance, suggesting leaks. After proximal control of the aorta was achieved, the anterior wall of the aneurysm was incised and the lumen of the aorta was entered. The aneurysm measured about 3.5 cm. However, there were two communicating holes, one on each side, leading to the retroperitoneal area. Large retroperitoneal hematomas were present, estimated to contain about 600 cc of blood. After resection of the major portion of the aneurysm a woven Dacron graft was used to restore aorta-to-iliac artery continuity. There were multiple enlarged lymph nodes located at the posterior part of the peritoneal area, and the tissues around the posterior parietal peritoneum were thickened and edematous. A cholecystectomy was performed because of previous history of Salmonella infection six weeks prior to admission. No operative difficulties were encountered.

Pathology: Five specimens were sent for pathologic analysis. 1. Periaortic node: nonspecific lymphadenitis. A few poorly formed granulomas were present. Gram stains revealed no organism on smears or section. 2. Anterior wall of aneurysm: extensive medial necrosis with hemorrhage and thrombosis along with infiltration by neutrophils, forming a microabscess. Elastic fragmentation were prominent. Hemosiderin deposition and infiltration with lymphocytes, plasma cells and macrophages were present. Gram stains of smears or sections revealed no organism. However, cultures were positive for Salmonella choleraesuis. 3. Tissue from an unspecified site of aorta: media and intima with marked necrosis, hemorrhage and atheromatous deposits. Cultures also revealed Salmonella choleraesuis. 4. Gallbladder: minimal Cholecystitis. Gram stains were negative. Cultures showed growth of Salmonella choleraesuis. 5. Unspecified blood clot: thrombus. Gram stains were negative.

Postoperative course: The postoperative course was uneventful other than an episode of angina which was later resolved. The patient was on ampicillin, chloromycetin, and Ancef. In view of his chronic septicemia, it was planned to place him on life-long antibiotic therapy with ampicillin.

Salmonella Infections

Salmonella belongs to the family Enterobacteriaceae. The overall incidence of salmonellosis in the United States is 10.4 per 100,000 population. Salmonella typhimurium and S. enteritidis comprised 29.8% and 5.2% respectively out of ten most frequently reported serotypes isolated from humans (2). S. choleraesuis, reported in the present case, though an uncommon cause of salmonella infections, has a high incidence in aortic endovasculitis and aneurysms. Six out of the twenty-five reported cases of salmonella infected abdominal aneurysm were identified to be caused by S. choleraesuis.

The usual portal of entry is the gastrointestinal tract. The signs and symptoms of salmonellosis are usually: gastroenteritis, bacteremia with or without extraintestinal localization, typhoidlike pattern (enteric fever) and a carrier state (either convalescent or asymptomatic). Patients with bacteremia frequently show absence of initial intestinal involvement and subsequent localization may occur. S. choleraesuis is most frequently isolated in the bacteremia. The organisms are widely disseminated and tend to cause focal suppuration, abscess, meningitis, osteomyelitis, pneumonia, endocarditis. In carriers, the organisms may reside in the intestine or in the gallbladder.

Pathogenesis (2, 6–9)

The pathogenesis of localized infection in the arterial wall occurs in four ways. The first mechanism, which has been reported to account for 80% of infected aneurysms, involves septic embolization within the arterial lumen usually from bacterial endocarditis or endovasculitis elsewhere in the cardiovascular system. There follows a gradual weakening with enlargement of the artery and aneurysm formation. The second mechanism is the extension from an adjacent inflammatory process either directly, most notably lumbar osteomyelitis secondary to pressure necrosis of the vertebral bodies caused by transmitted pulsations of the aneurysm, or by way of perivascular lymphatics, from a localized abscess or area of cellulitis which destroys the arterial wall causing massive bleeding or the formation of a pseudoaneurysm. The third mechanism involves lodgement of bacteria onto a diseased and roughened atherosclerotic intimal surface. This initiates a localized suppurative process in the aortic wall that weakens or destroys the media or allows formation of an aneurysm. The fourth mechanism is an injury to an artery associated with contamination and subsequent formation of a pseudoaneurysm. This usually occurs from external trauma or during vascular operations. In contrast to the other three mechanisms, this process represents a poorly contained infection with more diffuse inflammation of the surrounding soft tissues.

The possible mechanism in the present case, as in the majority of the reported cases, falls into either the second or the third category. As in all the other twenty-five cases of Salmonellosis with abdominal aneurysm, the patient is elderly with atherosclerosis. Salmonella seem to produce three types of vascular lesions: diffuse suppurative arteritis with rupture and development of a saccular or false aneurysm, focal arteritis with aneurysm formation and rupture, as well as secondary infection superimposed on a pre-existing arteriosclerotic aneurysm. Any of these three lesions is possible in this case, although the degenerative pathology of the aneurysm tends to point to the last process.

The patient presented with pneumonia plus lower back and abdominal pain associated with salmonellosis during his first admission. He was then treated for pneumonia and septicemia. However, his symptoms of lower back and abdominal pains imply a slowly leaking ruptured aneurysm. Even though the blood cultures were negative for salmonella at the second admission six weeks later, the bacteria might already have lodged onto the roughened atherosclerotic intimal surface of the aneurysm. This focus of bacteria initiated a localized suppurative process in the aortic wall which weakened the media, allowing the formation of a pseudoaneurysm, with subsequent bleeding into a hematoma retroperitoneally.

Cultures from the aorta, the aneurysm and the gallbladder showed growth of Salmonella cholerasuis. This indicates that the gallbladder is probably the source of salmonella. However, gram stains of smears and sections revealed no organism. It seems to imply that the salmonellosis was controlled by antibiotics temporarily during the patient's first admission, but not long enough to eliminate all the organisms. The bacteria had already damaged the aortic wall causing a slow rupture. The aneurysm and its thrombus-filled lumen provide an excellent culture medium. Antibiotics do not penetrate through the wall of the sclerotic aneurysm or through infected hematomas to any significant degree.

Clinical Presentations and Diagnosis

There are few signs or symptoms to indicate the diagnosis of infected aortic aneurysm, even after rupture occurs. The clinical picture may be dominated by symptoms related to the presence of the aneurysm or to its leakage or rupture. It may be that of chronic sepsis. The location of the aneurysm sometimes made palpation of the lesion impossible.

The importance of early diagnosis, however, is emphasized by the death of ten out of the 25 patients reported prior to any operative intervention (6). Bennett and Cherry (3) revealed that 79% of the patients with infected aortic aneurysm ruptured before the diagnosis was suspected. A triad of unexplained fever, back pain and pulsatile abdominal mass should suggest the presence of an infected abdominal aortic aneurysm. In the twenty-five reported cases of salmonellosis of the abdominal aorta, the triad was complete in 50%. The one common demoniator was the presence of fever, which occurred in all but one patient. Fever of unknown origin therefore should alert the physician to the possibility of an infected abdominal aortic aneurysm in patients at risk.

In all cases, the patient is elderly and is affected by other chronic diseases which can easily altered the clinical suspicion. In this case, the patient's chronic history of lumbosaccral arthritis and chronic obstructive lung disease masked his symptoms of fever and back pain. Together with the absence of an abdominal pulsatile mass, the infected ruptured abdominal aneurysm was overlooked. Ultrasonography is proven to be immensely useful in this case. In evaluating the presence of aortic involvement in patients with fever and back pain, ultrasonography may be a useful screening test.

Treatment

Antibiotics are an essential part of therapy of aortic salmonellosis. Appropriate antibiotic treatment should start before surgery and usually continue for six weeks, postoperatively (7). The most effective antibiotics against Salmonella are ampicillin and chloramphenicol, which can produce temporary sterilization of the blood stream. Continued destruction of the arterial wall, even though the blood culture is negative and relapse with fever and abdominal pain are to be expected after antibiotics are discontinued, as in this case. Cholecystectomy is indicated immediately if the gallbladder is inflamed or at a later date if the bile cultures grow Salmonella.

Excision of all infected tissues and foreign bodies with adequate drainage is essential to control the infection. Arteries should be ligated and a bypass procedure done only where the vessel is healthy and uninfected. Otherwise, infection will persist with eventual necrosis of the artery and rebleeding. Seven out of the 25 reported cases (6) who survived with aortic bypass grafting procedure, all died from recurrent infections, anastomatic leakage or overwhelming graft sepsis. Apparently, the vascular prothesis placed in an infected area frequently leads to reinfection. The retroperitoneal area for some reason favors the growth of enteric pathogens.

The general opinion (6–8) for effective surgical treatment depends on total excision of the involved vessel and wide debridement of the retroperitoneum with a bypass procedure through noninfected tissue planes. Placement of a prosthetic graft in an infected bed, results in persistent retroperitoneal infection and eventual anastomotic failure necessitating removal of the prosthesis irrespective of the use of antibiotics and irrigations. Both axillofemoral and thoracic bifemoral bypasses have been used. Wilson et al (11) suggested a unilateral axillofemoral bypass combined with a femoral-femoral bypass, which is believed to be superior to bilateral axillofemoral bypass because of its higher flow rate and patency.

It is recommended (6, 12) that for elective repair of abdominal aortic salmonellosis, a clean bypass to the lower extremities be performed before ressection of the infected area. To illustrate the surgical technique, two cases reported by Scher et al (12) are reviewed. After a correct diagnosis was made preoperatively, a preliminary axillofemoral bypass was performed. A clamp was applied to the common femoral artery above the axillofemoral anastomosis before aortic occlusion to avoid competitive aortoiliac flow and potential intraoperative graft occlusion. The aortic bifurcation was removed to ensure complete removal of the infection. The common iliac arteries were anastomosed to each other as an internal crossover. The femoral clamp was then removed.

In emergency treatment of aortic rupture with salmonellosis, a primary graft to control the ruptured area is necessary. The aorta should be closed wrapped with omentum and wide excision of the retroperitoneum. Antibiotics should be given for six months postoperatively to sterilize the retroperitoneum and blood stream, followed by secondary reconstruction with aortic-bifemoral grafting. In the present case, the patient's ruptured aneurysm was replaced with a Dacron graft. He will be followed carefully to determine if a secondary reconstruction is necessary in the future.

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Unusual Roentgenographic Appearance of a Pseudotumor in the Pleural Space: A Case Report

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Abstract

An 84-year-old man with congestive heart failure was found to have an enlarging pleural mass over a one-year period. The absence of relationship of the mass to any interlobar fissure led physicians to believe that the mass was caused by a neoplasm. It was only after the density disappeared following diuretic therapy that the true diagnosis of "pseudotumor" became apparent. A literature review failed to reveal any previous reports of a pseudotumor that did not in some way involve an interlobar fissure.

Pleural fluid accumulation secondary to congestive heart failure occasionally localizes in a pleural space in such a configuration as to simulate a neoplasm. The terms "vanishing tumor," "pseudotumor," and "phantom tumor" have been applied to this condition, since the collection generally disappears following treatment for the heart failure. Most often, these focal collections are recognized in interlobar fissures or in sites where interlobar fissures join the lateral pleural space, and the underlying process is apparent. In this report, we describe a patient with an enlarging pleural mass over a one-year period that was considered to be a neoplasm because it was unrelated to any interlobar fissure on chest roentgenograms. Disappearance of the mass following treatment for congestive heart failure revealed the correct diagnosis of pseudotumor.

Case Report

An 82-year-old male entered the hospital for evaluation of a pleural mass that had been enlarging for one year. He smoked cigarettes for many years but stopped 12 years previously because of exertional dyspnea and chronic cough. For several months he had been aware of ankle edema, progressive shortness of breath and weight gain. Other medical problems included hypertension, chronic alcoholism and idiopathic osteopenia for which he had been taking NaF and $CaCO_3$ for six years.

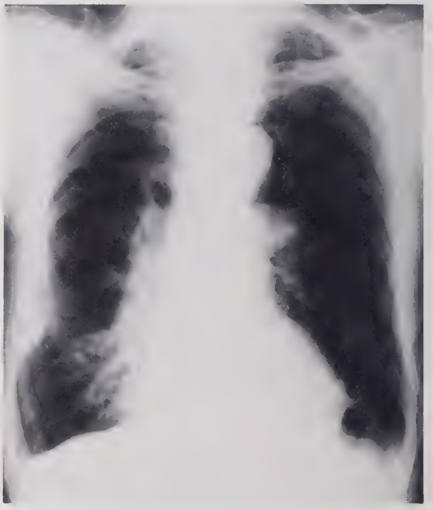

FIG. 1. Chest roentgenogram taken one year before admission shows prominent pulmonary vessels, bullous changes in the left lower lobe, hilar fullness on the right, blunted costophrenic angles and a homogeneous density in the right lateral chest.

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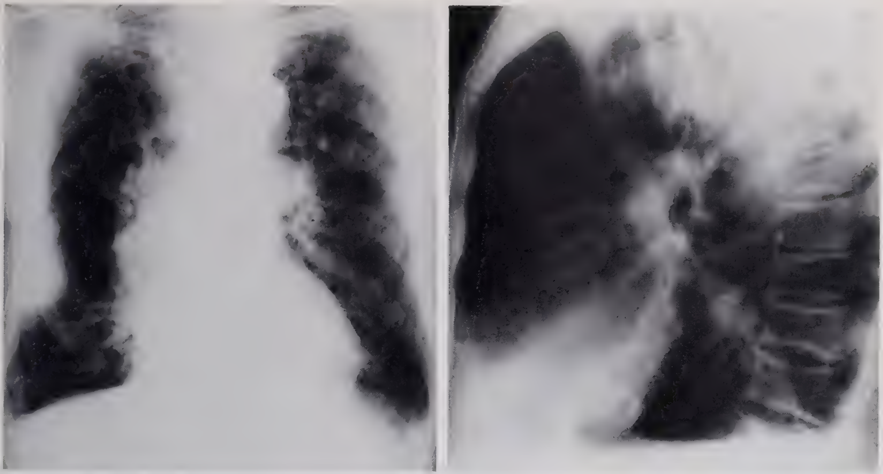


FIG. 2. Admission chest roentgenograms show enlargement of the homogeneous density. The homogeneous mass is not present in any interlobar fissure.

Physical examination revealed a cachetic male in moderate respiratory distress. The neck veins were distended while the patient was sitting at 45°, and the lung examination revealed bilateral basilar rales and diffuse wheezing. He had pitting edema of the lower extremities up to the knees. Cardiac examination revealed no murmurs or gallops.

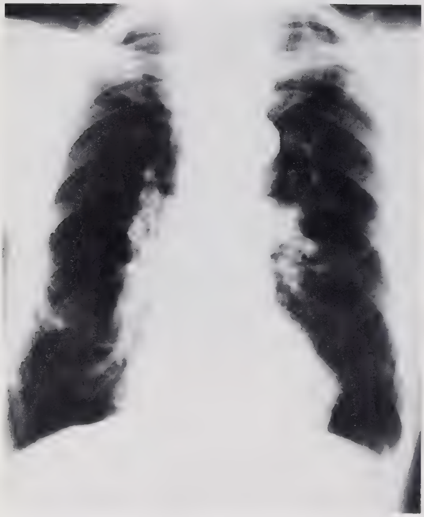
Laboratory studies included an electrocardiogram that showed a rate of 100 with right bundle branch block and poor R wave progression. Arterial blood revealed a pH of 7.40, a PO_2 of 47mmHg and a PCO_2 of 38mmHg. A chest roentgenogram revealed slight cardiomegaly, prominent pulmonary vasculature, flattened diaphragms with blunting of the costophrenic angles, and a right pleural mass that had increased in size over a one-year period (Figs. 1, 2). The mass lesion was not apparent on a lateral roentgenogram (Fig. 3). Oblique roentgenograms suggested that the mass was posterior and unrelated to interlobar fissures.

The initial impression was decompensated left ventricular heart failure, severe chronic bronchitis and emphysema, and a right pleural mass possibly representing a neoplasm. The patient was treated with bronchodilators and a diuretic with decrease in shortness of breath and ankle edema over the next few days. A repeat chest roentgenogram on the 12th hospital day revealed that the pulmonary vasculature was less congested and the pleural mass was no longer present (Figs. 3A, 3B).

Discussion

The patient was noted to have a discrete pleural mass on frontal chest roentgenograms that had been enlarging over the course of one year. Although he also had clinical and roentgenographic findings of left ventricular failure, the peripheral location of the pleural density, and its lack of relationship to any interlobar fissure on lateral chest roentgenograms, suggested that the process was due to a neoplasm rather than to a loculated pleural effusion secondary to heart failure. It was only after the pleural mass disappeared with diuretic therapy that the correct diagnosis of pseudotumor was appreciated and the patient was spared a diagnostic work-up.

Although pleural effusions associated with congestive heart failure typically accumulate in the dependent portions of the free pleural cavities, occasionally, fluid may localize in the transverse fissure of the right lung or, less often, in either oblique fissure (1, 2). When this occurs, the interlobar collection usually assumes a circular or oblong configuration that has been frequently entitled "pseudotumor," "phantom tumor" or "vanishing tumor," because of a strong resemblance to a true neoplastic process. Loculated accumulations of pleural fluid in the lateral pleural space are rarely confused with neoplasms because, generally, fluid simultaneously protrudes into the lateral end of the transverse fissure or is also associated with fluid within the depen-



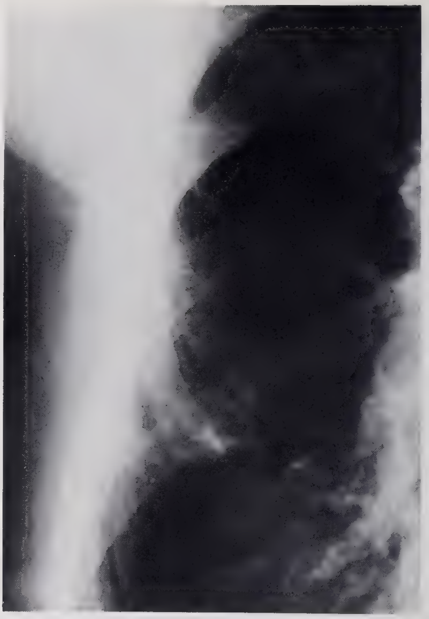


FIG. 3A. Chest roentgenogram shows that the homogeneous mass has disappeared.
FIG. 3B. More detailed view to confirm disappearance of mass density.

dent portions of the same pleural space (3, 4). A focal accumulation of pleural fluid in the lateral pleural space secondary to congestive heart failure without relationship to an interlobar fissure or obvious free fluid in the pleural space, as observed in our patient, has not been previously described.

The mechanisms involved leading to loculated accumulations of pleural fluid secondary to congestive heart failure have not been thoroughly explored. Based upon autopsy findings, it has been proposed that underlying obliterative pleuritis secondary to previous infectious processes defines and limits the space available for fluid accumulation (1). However, observations that interlobar effusions can develop in association with free fluid in the pleural cavity suggests that adhesive pleuritis may not always be necessary (5). In our patient, definitive information explaining the unusual fluid collection process is lacking, but underlying obliterative pleuritis seems to be the most likely explanation, since both costophrenic angles on roentgenograms were blunted even after diuresis, suggesting a chronic pleural process.

The major clinical considerations related to homogeneous densities within the lung or pleural space are usually whether the mass represents a neoplasm or inflammatory process. If findings of congestive failure are present and the density is in or related to an interlobar fissure, the correct diagnosis is usually apparent and diuretic therapy successfully induces resolution. If, however, as demonstrated by the patient described in this report, the major roentgenographic findings of loculated effusions are lacking, pseudotumor may not be considered in the differential and invasive diagnostic manuevers may be considered or undertaken.

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Radiologic Notes

Claude Bloch, M.D. and Harvey Peck, M.D., Coeditors

Multinodular Thoracic Densities in an Ex-shipyard Worker

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Case Report

A sixty-five-year old white male was found to have an abnormal chest radiogram on routine examination (Fig. 1). He had no pulmonary symptoms, and was never a cigarette smoker. During World War II, he worked as a pipe fitter in the Brooklyn Naval Shipyard.

Physical examination was normal except for bilateral carpal tunnel syndrome. Complete blood count and chemistries were within normal limits.

Because of the chest roentgenogram findings and his occupational history, a computed tomography (C-T) of the chest was performed (Fig. 2). The patient was referred for diagnostic flexible fiberoptic bronchoscopy.

Diagnosis: Pleural Plaques

The chest roentgenogram showed bilateral pleural scalloping. A 2 cm well circumscribed and a 3 cm ill-defined density were seen at the left second and third anterior interspaces, respectively. The roentgenogram findings are compatible with pleural disease due to asbestos exposure. The nodular density at the left second anterior interspace, however, could be a pulmonary neoplasm. Even though the patient is a nonsmoker, the incidence of lung cancer in patients with asbestos exposure is more than 5 times that of controls (1). The C-T of the chest (Fig. 2) clearly shows a 2 cm intrapulmonary nodule in the left upper lobe plus a 3 cm pleural density in the right upper lung field.

During bronchoscopy, the lesion appeared to be related closely to the second anterior interspace on fluoroscopy. The brush could not be advanced into the lesion, always passing posterior to the lesion. A pleural process rather than an intrapulmonary lesion was suspected. A diagnostic pneumothorax demonstrated that the lesion was indeed a pleural plaque as seen on the post-pneumothorax chest film (Fig. 3).

A left thoracoscopy with biopsy confirmed the diagnosis.

A pleural plaque is an aggregate of benign fibrohyalinized connective tissue arising in the parietal pleura. Commonly seen in workers with prolonged exposure to asbestos, the incidence is 2%–21% depending on the duration and type of exposure (2, 3). Similar pleural lesions are seen in patients with a previous history of chest trauma, empyema or pleural tuberculosis. These are often calcified and unilateral and the dependent portion (costophrenic angle) is usually involved. Pleural plaques of asbestosis are usually bilateral and may also be calcified, occasionally the chest roentgenographic appearance may simulate lung tumor and confuse the diagnosis (4).

Although C-T of the chest is more accurate for detecting pulmonary nodules than conventional chest roentgenography or whole-lung tomography, false-positive and false-negative studies have been reported, in 6% and 8% of cases, respectively (5). This case demonstrates that a pedunculated pleural lesion may be mistaken for an in-

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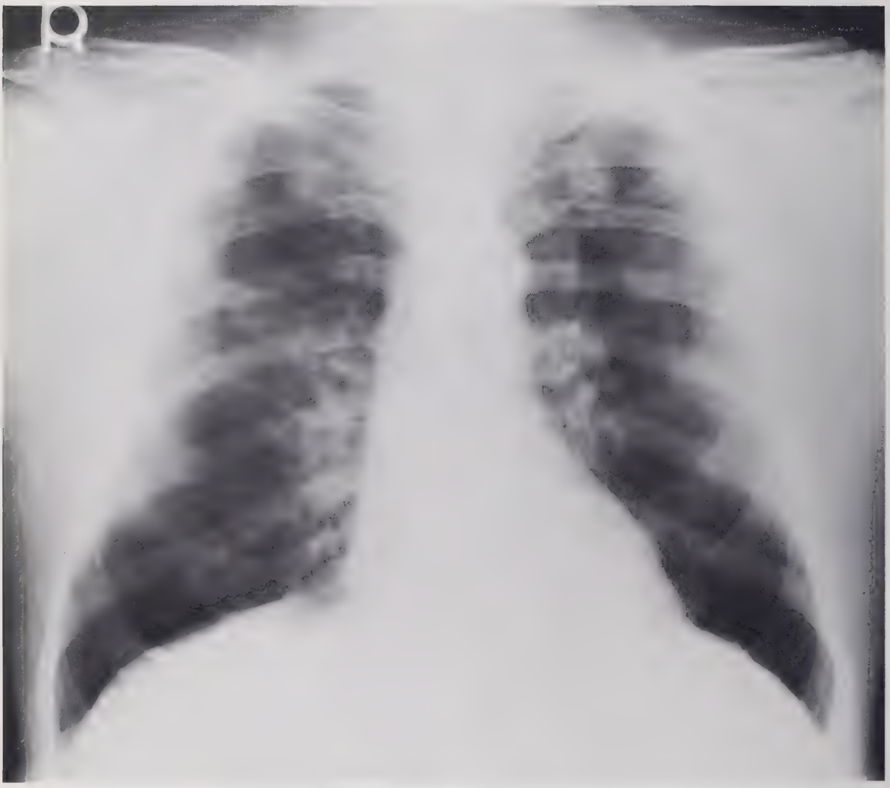

FIG. 1. Chest roentgenogram, P-A projection.

trapulmonary lesion on C-T of the chest. Diagnostic pneumothorax coupled with thoracoscopy will establish the diagnosis.

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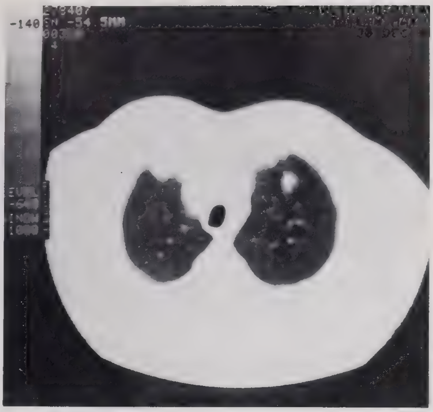

FIG. 2. C-T scan of thorax.

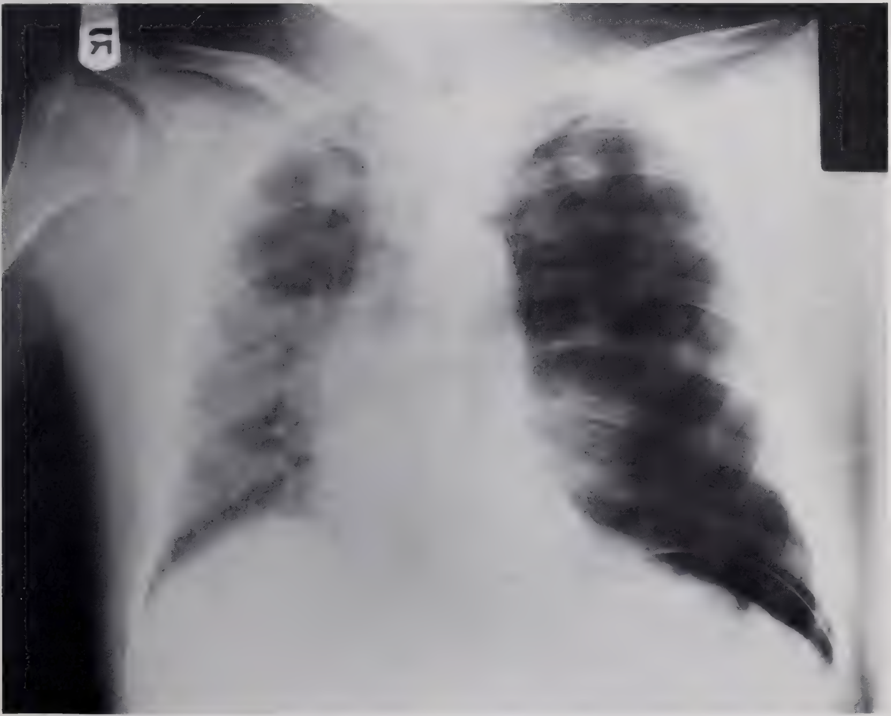

FIG. 3. Chest roentgenogram, P-A projection with diagnostic left pneumothorax.

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Galactorrhea, Amenorrhea, Hyperprolactinemia and Pseudotumor Cerebri in a Patient with Primary Empty Sella Syndrome: Case Report with Review of the Literature

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Abstract

A 22-year-old female with a primary empty sella syndrome (PESS) presented with galactorrhea, amenorrhea, hyperprolactinemia and visual impairment following a history of pseudotumor cerebri. Chiasmapexy was performed and no demonstrable evidence of an associated pituitary-secreting adenoma was found. Thyroid releasing hormone (TRH) and chlorpromazine testing was suggestive of hypothalamic dysfunction. Postoperatively the hyperprolactinemia persisted with associated oligomenorrhea. The mechanisms involved for galactorrhea and/or hyperprolactinemia in the primary empty sella syndrome are discussed.

Amenorrhea, galactorrhea and hyperprolactinemia are frequently associated with prolactin-secreting pituitary tumors (24, 31), most of which can be detected with newer computerized axial tomographic techniques. Galactorrhea with or without hyperprolactinemia or amenorrhea has been described in instances of primary empty sella syndrome (PESS) (3, 5–7, 9, 17–19, 22, 24, 25, 30). Several reports describe the association of primary empty sella syndrome with prolactin-secreting pituitary tumors (2, 10, 21, 23, 30, 34–36), acromegaly (10, 21, 27, 28, 34), and Cushing's syndrome (16). It is the purpose of this paper to report the association of galactorrhea, amenorrhea, and hyperprolactinemia in a patient with prior history of visual impairment secondary to pseudotumor cerebri, who subsequently underwent chiasmapexy. Results of endocrine studies including TRH (thyroid releasing hormone), computerized axial tomography (CAT) and operative findings tended to exclude an associated pituitary microadenoma. Possible explanations for the clinical findings in our patient are discussed with a review of galactorrhea, amenorrhea and hyperprolactinemia which may mimic a pituitary tumor, but which also may be associated with PESS.

Case Report

A 22-year-old black female was admitted to The Mount Sinai Hospital on September 3, 1978 for evaluation of secondary amenorrhea following a normal full term spontaneous delivery of her only child August 6, 1977. Associated with the postpartum amenorrhea, she noted bilateral galactorrhea and a 50-pound weight gain. Past history revealed onset of menarche at 11 years of age with regular menses at 28-day intervals lasting for five days. In 1972, a diagnosis of pseudotumor cerebri was made with impairment of vision in both eyes. Three episodes of severe headaches with vomiting followed by horizontal diplopia were described from 1972–1974 and on each occasion she responded well to steroids. Angiograms at that time were entirely normal. Six months prior to her present admission, she experienced

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impairment of vision in both eyes, the left more than the right eye. She denied drug ingestion, somnolence, polydypsia, acral changes, headaches, reduced libido or hirsutism. The family history was noncontributory. Pertinent physical findings revealed a clinically euthyroid female with generalized obesity weighing 252 pounds with a height of 62 inches. Both optic disks were pale with only temporal paracentral islands of vision in each eye. Best correction of the right eye was 10/400 while that of the left eye was 3/400. Both breasts demonstrated a milky discharge on minimal expression. No thyromegaly, acne, hirsutism or violaceous striae were present. Her blood pressure was 100/64 mm. Pelvic examination was within normal limits.

Routine chemistries were normal. Serum prolactin levels were 44.8 and 90.0 ng/ml. The remaining endocrine studies are summarized in Table I.

Sella turcica views revealed a deepened floor of the sella turcica with erosion and decalcification. The vertical diameter of the sella turcica was 17 mm while the AP diameter was also 17 mm. Hypocycloid polytomography of the sella turcica revealed the floor to be depressed and eroded. The dorsum sellae also showed extensive erosion. Fractional pneumoencephalography revealed no evidence of a suprasellar mass. However, the suprasellar subarachnoid space was seen to be extending into the sella turcica. Computerized axial tomography (CAT) revealed diffuse lucency of the intrasellar region with no evidence of pituitary tumor.

On September 14, 1978 chiasmapexy with fascia lata graft was performed. The subarachnoid cyst was displaced superiorly by the procedure, with no complications utilizing the transsphenoidal approach. Biopsy of the pituitary gland revealed normal tissue. Three months later menses resumed at 1–2 month intervals with a five-day flow. Galactorrhea ceased prior to resumption of menses. No significant postoperative visual changes were noted. Postoperative endocrine studies including TRH and chlorpromazine testing are summarized in Tables II and III.

TABLE I

Preoperative Endocrinologic Studies

Serum T4	8.1 μg/100 ml
Serum TSH	3.5 uIU/ml
Plasma cortisol	14.0 μg/100 ml
Serum growth hormone	3.1 ng/ml
Serum dehyroepiandrosterone sulfate (DHA-S)	140.0 μg/100 ml
Serum prolactin	44.8 ng/ml 90.0 ng/ml
Serum estradiol	5.4 ng/100 ml
Serum LH*	1.7 mIU/ml
Serum FSH**	2.9 mIU/ml
Urinary 17-ketosteroids	11.8 mg/24 hr

* Normal value at follicular phase of cycle = 0.6–2.8 mIU/ml

** Normal value at follicular phase of cycle = 2.7–7.4 mIU/ml

TABLE II

Postoperative Endocrinologic Studies

9/14/78	Serum prolactin	60.0 ng/ml
	Serum T4	7.1 μg/ml
	Serum TSH	1.3 uIU/ml
	Serum estradiol	1.3 ng/100 ml
	Serum LH	0.5 mIU/ml
	Serum FSH	1.0 mIU/ml
10/19/78	Serum prolactin	47.0 ng/ml
	Serum T3-RIA	131.0 ng/100 ml
4/3/79	Serum prolactin	54.5 ng/ml
11/9/79	Serum T4	6.0 μg/100 ml
	Serum prolactin	58.9 ng/ml
2/25/80	Serum prolactin	65.0 ng/ml
	Serum progesterone	0.8 ng/ml***

*** Normal value at luteal phase of cycle = 1.0–26.0 ng/ml

Discussion

Our patient had the unique association of a primary empty sella syndrome with (1) galactorrhea, (2) amenorrhea, (3) hyperprolactinemia, (4) visual impairment and optic atrophy following (5) a history of pseudotumor cerebri. Chiasmapexy performed via a transsphenoidal approach was followed by resumption of irregular menses, cessation of galactorrhea, but persistence of hyperprolactinemia. CAT scan, operative inspection of the pituitary remnant, pituitary biopsy and dynamic testing with TRH made the possibility of an associated prolactin-secreting microadenoma unlikely as the cause of the persistent hyperprolactinemia.

Galactorrhea and/or amenorrhea has been described in the PESS (2, 3, 5–7, 9, 17–19, 21, 22, 24, 25, 30), although in a series of 31 cases of empty sella syndrome reported by Neelon et al (28) none had galactorrhea. Bryner et al (6) reported eight instances of galactorrhea in a series of 115 patients with a diagnosis of empty sella syndrome made on the basis of polytome pneumoencephalography. Four of these eight patients had associated amenorrhea and two had elevated serum prolactin levels of 64.5 and 81 ng/ml. Of interest was the finding of elevated spinal fluid pressure in three normoprolactinemic patients with galactorrhea and empty sella syndrome, and a low anterior third ventricle in six of the eight

TABLE III

*Results of TRH and Chlorpromazine (CPZ) Testing 1/28/81**

Min.	Serum TSH (uIU/ml)	Serum Prolactin (ng/ml)
0	3.3	56.0
500 µg TRH iv		
15	14.0	136.0
30	15.0	160.0
60	11.5	124.0
90	8.5	102.0
0	7.5	76.0
50 mg. CPZ im		
30		76.0
60		64.0
120		76.0
180		70.0
240		60.0

* A normal adult female response to both TRH and CPZ causes at least a two-fold increase of basal prolactin

patients with galactorrhea (6). In another series of 50 patients with PESS by Brismar and Efendic (5), five women and one man were hyperprolactinemic with a range of serum prolactin of 40–99 ng/ml. Four of the five women were also amenorrheic with associated galactorrhea, and evidence of increased intracranial pressure was noted in three of these five women (5). Although the majority of patients with PESS and/or galactorrhea are associated with normal levels of serum prolactin (5, 17, 22, 24, 29, 30, 32), those with galactorrhea usually have associated oligo- or amenorrhea (5–7, 9, 18, 22, 30). The data in the literature are not always clear as to whether an associated prolactin producing microadenoma was entirely excluded in those instances of galactorrhea associated with hyperprolactinemia in the PESS (2, 6, 7, 9, 19, 25). It appears likely that an associated prolactin secreting pituitary adenoma may have been present in those instances with serum prolactin levels over 325 ng/ml. (2, 18, 19). The association of PESS with functional pituitary tumors secreting prolactin or growth hormone has been described as 17.3 and 10 percent, respectively (10). A number of reports describing the association of empty sella syndrome with secretory pituitary tumors have stressed the importance of incidental pathology as probably being responsible for most instances of endocrine dysfunction (2, 16, 23, 27, 28, 30, 32, 34).

The endocrine abnormalities found in the PESS, although infrequent, are quite variable. These may include impairment of growth hormone response to insulin (which, in part, may be related to the frequently associated obesity), blunted plasma cortisol response to insulin induced hypoglycemia, and isolated instances of reduction of gonadotropins, secondary hypothyroidism, diabetes insipidus and hypopituitarism (4, 5, 11, 12, 28, 30). Some of these are related to associated abnormalities of the hypothalamus and adenohypophysis (5, 23, 28, 30). Dynamic testing of the adenohypophysis with gonadotropin hormone releasing hormone (GHRH) and the TSH response to thyroid releasing hormone (TRH) are usually normal (8, 12, 17, 23, 24, 29, 30, 32). Several patients with PESS have been reported to demonstrate hyporesponsiveness of TSH to TRH (12, 13, 30). Most patients with PESS are normoprolactinemic and their serum prolactin response to TRH is normal (17, 23, 24, 29, 30, 32), with a two-fold or greater increase in serum prolactin over basal levels (29). Occasional normoprolactinemic patients with PESS do not demonstrate a normal doubling or more of the prolactin following TRH testing (17, 24, 30). Other than several patients with markedly elevated serum prolactin levels who probably had associated pituitary microadenomas and who failed to respond to TRH, (2, 19) there are no reports to date of the response of hyperprolactinemic subjects with PESS who were tested with TRH.

Despite normal responsiveness of our patient to TRH, there was no response of her serum prolactin to the intra-muscular administration of 50 mg chlorpromazine (CPZ) (Table III). Four of five normoprolactinemic patients with PESS and galactorrhea reported in the literature (3, 24) also failed to double basal serum prolactin levels following injection of 25 mg CPZ, while suppressing normally to a standard L-dopa test. One hyperprolactinemic subject (77 ng/ml) with PESS was nonresponsive to CPZ (7). Although absence of a prolactin surge following CPZ can occur in a variety of hypothalamic-pituitary disorders (1), its occurrence in the presence of prolactin responsiveness to TRH is highly suggestive of hypothalamic dysfunction (15). The frequent finding of CPZ unresponsiveness in such patients suggests possible hypothalamic dysfunction. CPZ is a nonspecific dopamine receptor antagonist, not only blocking dopamine receptors on pituitary lactotrophs but on hypothalamic receptors as well.

Normal pituitary lactotroph responsiveness to TRH in our patient and others with PESS with galactorrhea and amenorrhea is well documented. Galactorrhea with or without hyperprolactinemia in patients with PESS may represent a "marker" of hypothalamic dysfunction in such patients. Indeed, the presence of galactorrhea without hyperprolactinemia is well known and of frequent occurrence (26). The presence and persistence of the hyperprolactinemia with oligomenorrhea postoperatively in our patient without obvious evidence of an associated pituitary prolactin-secreting microadenoma, makes it likely that the galactorrhea and hyperprolactinemia was of hypothalamic origin. Instances of other hypothalamic disorders which may cause hyperprolactinemia and/or galactorrhea include sarcoidosis, craniopharyngiomas, histiocytosis and hemochromatosis (20).

Bryner et al (6) as well as Brismar and Efendic (5) have speculated that hypothalamic dysfunction in instances of PESS and galactorrhea and/or hyperprolactinemia may occur in this syndrome. Compression of the hypothalamus or pituitary stalk may occur as a result of elevated CSF pressure and an associated low anterior end of the third ventricle. Compression or kinking of the pituitary stalk or even impairment of its blood supply may thus result. Increased intracranial pressure was found in 24 of 50 patients with PESS described by Brismar and Efendic (5), with three of six of their patients with hyperprolactinemia demonstrating this sign. Distortion of the infundibular stalk with extensive intrasellar cisternal herniation further compromises transport or release of prolactin inhibitory factor (PIF) that reaches the pituitary. The persistence of hyperprolactinemia after chiasmapexy in two of three patients described by Haney et al (18), as in our patient, makes a hypothalamic defect in PESS associated with galactorrhea or hyperprolactinemia quite probable.

The finding of visual impairment with a history of pseudotumor cerebri in this patient is not uncommon in PESS. The incidence of increased CSF pressure in the empty sella syndrome varies from 10.5–65.0 percent (5, 14, 21, 23, 28). Most investigators agree that visual field defects and visual loss are more likely when pseudotumor cerebri and the PESS appear together than when either occurs independently (14). Chronic elevation of intracranial pressure could, in the presence of an incompetent diaphragmatic sella, produce herniation of the subarachnoid cistern into the sella turcica, with resultant flattening of the pituitary gland and sellar enlargement. The association of elevated intracranial pressure and an incompetent diaphragmatic sella causes greater likelihood of herniation and stretching of the optic nerves or chiasm. The clinical spectrum of benign intracranial hypertension may need redefining in view of a study by Spence et al (33) indicating possible absence of papilledema or visual loss in this entity.

The relatively common occurrence of PESS, particularly in obese multiparous females, should alert the physician to its possible presence even in instances of galactorrhea, amenorrhea, hyperprolactinemia and visual disturbances. Appropriate testing with more refined computerized axial tomographic techniques, particularly with coronal sections, may sometimes demonstrate the PESS and further endocrine testing with TRH and CPZ may yield additional data suggesting the diagnosis of PESS.

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